

**Cough Reflex Following Orotracheal Intubation: Presence
and recovery of the cough reflex after extubation and validity of
Cough Reflex Testing**

A thesis submitted in partial fulfilment of the requirements for the Degree
of Doctor of Philosophy in Speech and Language Pathology at the University of
Canterbury

by

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PREFACE

This PhD thesis conforms to the referencing style recommended by the American Psychological Association Publication Manual (6th ed.) and spelling recommended by the Oxford English Dictionary.

The research was carried out between February 2013 and August 2015 at Capital and Coast District Health Board in Wellington, New Zealand. The research was supervised by Prof. Maggie-Lee Huckabee, The University of Canterbury and Dr. Alex Psirides, Intensivist, Wellington Hospital ICU, Capital and Coast District Health Board. Citric acid solutions for Study I and Study II were donated by Optimus Healthcare Ltd.. VES equipment was provided on loan by Olympus Ltd. and Tristel wipes were donated for cleaning the endoscope by Tristel Solutions Ltd.

Preliminary results from this PhD research have been presented at the following national and international conferences:

- Kallesen, M., Psirides, A. & Huckabee, M. L. (2013). A prospective study of cough response to nebulised citric acid following intubation. Platform presentation. 6th Biomouth Symposium, Dunedin, New Zealand, 9th October 2013.
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ABSTRACT

Post-extubation dysphagia is well documented in the Intensive Care Unit (ICU) population, particularly following prolonged intubation (≥ 48 hours). Identifying patients with dysphagia is important as these individuals are more likely to develop pneumonia, and ICU patients who develop pneumonia are more likely to have poor outcomes. Despite the frequency and clinical significance of post-extubation dysphagia, there are currently no recognised, standard protocols outlining how and when to assess swallowing in patients after extubation. Assessing swallowing in this population is complicated by the high prevalence of silent aspiration, which cannot be identified on clinical assessment.

Silent aspiration has been associated with attenuation of the cough reflex in the stroke population and cough reflex testing (CRT) has shown promise as a screening tool to identify patients who are at risk of silent aspiration. There is evidence in the literature that the cough reflex is impaired following short periods of orotracheal intubation for minor surgery, but the cough reflex has never been studied specifically in the post-extubation ICU population. Thus, it may be hypothesised that CRT is a suitable tool for assessing the cough reflex following extubation and may also be able to identify which patients are at the greatest risk of silent aspiration.

This research programme investigated the impact of orotracheal intubation on the cough reflex. The goals of Study I were to identify and quantify impairment of the cough reflex following extubation and to track recovery of the cough reflex. Eighty-six participants who were admitted for elective coronary artery bypass grafting (CABG) underwent CRT prior to intubation using 0.4, 0.8 and 1.2 mol/L nebulised citric acid to establish baseline thresholds for reflexive cough. CRT was repeated within two hours of extubation to identify change from baseline cough. If a participant's cough sensitivity was at their pre-intubation baseline, their participation in the study was complete. Participants who had an absent cough

or required a stronger concentration of citric acid to stimulate cough were retested every morning and evening thereafter until they coughed at their baseline level, withdrew from the study or were discharged from hospital. Participants varied in time to recovery of cough reflex. Sixty percent of participants had an absent cough reflex at the first follow-up after extubation (M=70 minutes). By the fifth follow-up, which occurred at approximately 48 hours post-extubation, 86% of participants had recovered their baseline cough sensitivity. Age, gender and length of intubation had no significant impact on the time to recovery of cough reflex ($p>0.3$). There was a highly significant correlation between opioid dose and CRT result with participants with higher doses (mg/kg/hr) returning more quickly to baseline CRT. However, this was more likely due to the pattern of opioid administration, with patients passing the first CRT after extubation consistently having had higher recent opioid doses than patients passing on the fourth or fifth follow-up, rather than a causative relationship between high doses of opioids and increased cough sensitivity.

The primary aim of Study II was to determine the sensitivity and specificity of CRT for identifying silent aspiration. One hundred and six ICU patients underwent CRT using 0.4, 0.6 and 0.8 mol/L nebulised citric acid and videoendoscopic evaluation of swallowing (VES) within 24 hours of extubation. Cough reflex threshold was established for each participant and cough responses were classified as strong or weak. VES was recorded for later evaluation by a speech-language therapist (SLT) who was blinded to the results of CRT.

Thirty-nine (37%) participants had an absent cough to CRT. Thirteen (12%) participants aspirated on VES, 9 (69%) without a cough response. Sensitivity of CRT to identify silent aspiration was excellent at detecting both aspiration and silent aspiration at 0.4 and 0.6 mol/L nebulised citric acid, with weak cough responses grouped with absent responses. However, specificity of CRT to detect aspiration or silent aspiration was poor at all concentration and regardless of the grouping of weak cough responses with strong or

weak responses. There was a significant correlation between intubation duration and presence of aspiration on VES ($p=0.01$). There was no significant correlation between silent aspiration on VES and length of intubation or either overt or silent aspiration and age, gender, reason for ICU admission, indication for intubation, APACHE III score, morphine equivalent dose or time of testing post-extubation.

In summary, this research programme is the first to identify that cough reflex to citric acid is impaired following extubation and that this impairment often persists for up to 48 hours. It confirms that ICU patients are at risk of aspiration and silent aspiration following extubation, and provides new evidence that CRT has poor specificity when screening for silent aspiration risk in this population. This poor specificity suggests that the causes of post-extubation aspiration and post-extubation cough impairment differ. These results contribute to better understanding of post-extubation dysphagia. More research is needed to determine if CRT would be beneficial within particular patient groups after extubation and to determine the cause of post-extubation cough impairment.

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- In cases where the candidate was the lead author of the co-authored work he or she wrote the text

Name: Prof. Maggie-Lee Huckabee

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ABBREVIATIONS

AC	Ansa cervicalis
APACHEIII	Acute Physiology and Chronic Health Evaluation III
C2	2 coughs = pass
C5	5 coughs = pass
CABG	Coronary Artery Bypass Grafting
CIP	Critical Illness Polyneuropathy
CN	Cranial Nerve
CN I	Olfactory Nerve
CN II	Optic Nerve
CN V	Trigeminal Nerve
CN VII	Facial Nerve
CN IX	Glossopharyngeal Nerve
CN X	Vagus Nerve
CN XII	Hypoglossal Verve
CRT	Cough Reflex Testing
CRT1	Baseline CRT
CRT2	First CRT following extubation
CRT3-6	Follow-up CRTs
ED	Emergency Department
ERS	European Respiratory Society
ETT	Endotracheal Tube
FEES	Fiberoptic Endoscopic Evaluation of Swallowing
GCS	Glasgow Coma Scale
ICU	Intensive Care Unit

LMA	Laryngeal Mask Airway
mg/kg/hr	Milligrams per kilograms per hour
NA	Nucleus Ambiguus
NTS	Nucleus Tractus Solitarius
PAS	Penetration – Aspiration Scale
RAR	Rapidly Adapting Receptors
RLN	Recurrent Laryngeal Nerve
SAR	Slowly Adapting Receptor
SLN	Superior Laryngeal Nerve
SLT	Speech-language Therapist
UES	Upper Oesophageal Sphincter
VAP	Ventilator Associated Pneumonia
VES	Videoendoscopy of Swallowing
VFSS	Videofluoroscopy of Swallowing

PART A: INTRODUCTION & LITERATURE REVIEW

CHAPTER ONE

Introduction, Literature Review & Statement of the Problem

1 Introduction, Literature Review and Statement of the Problem

1.1 Introduction

Post-extubation dysphagia is common and patients who have been intubated are more likely to aspirate when eating and drinking (Ajemian, Nirmul, Anderson, Zirlen, & Kwasnik, 2001; El Solh, Okada, Bhat, & Pietrantonio, 2003; Leder, Cohn, & Moller, 1998; Scheel, Pisegna, McNally, Noordzij, & Langmore, 2016). Individuals who aspirate are more likely to have poor outcomes, including the development of pneumonia, longer stays in hospital and greater chance of death (Macht et al., 2011). Although this phenomenon is well recognised, there are currently no accepted protocols on how and when to assess swallowing in this population. Following extubation, some patients aspirate without producing a cough response (Ajemian et al., 2001; El Solh et al., 2003; Leder et al., 1998) and traditional clinical swallowing assessment is not able to reliably detect silent aspiration. Research into the use of cough reflex testing (CRT) to screen for risk of silent aspiration has shown promise in the stroke population and may be a useful tool for the post-extubation population. However, little is known about the effect of intubation on the cough reflex. This research programme will investigate the impact of orotracheal intubation on the cough reflex and the value of CRT in this population.

Following this brief introduction, Part A of this thesis explores the literature on normal and disordered swallowing in the intensive care unit (ICU) setting, specifically after extubation. In addition, the importance and mechanisms of airway protection and effect of intubation on the airway are outlined. Finally, existing research on CRT is explored in detail, including the various methodologies used by different research groups. This information lays the foundation for the methodology selected in the research programme.

In Part B, two original research projects are presented. The aims of the first project, Study I, were to identify and quantify impairment of cough reflex to citric acid following extubation and to track recovery of the cough reflex. The primary aim of the second study was to determine the sensitivity and specificity of CRT for detecting silent aspiration by analysing the correlation between response to CRT and response to aspiration on videoendoscopy (VES). The hypotheses of these two studies, research methodologies, analyses and results are presented.

In Part C, the results of the research programme are discussed in the context of related literature. These are the first studies to examine CRT in the post-extubation population and the significance of the new information is explored. The reasons for differences between validity results in this research programme and previous studies are debated. There are several limitations to the research studies presented in this thesis and these are also outlined.

Finally, Part D explores directions for future research. Both swallowing and cough reflex are impaired after extubation. Although CRT has poor specificity as a screening tool for silent aspiration in the ICU population, better understanding of how orotracheal intubation affects the cough reflex and swallowing and further attempts to develop valid assessment tools for this population will ensure that risk is minimised in this vulnerable group.

1.2 Normal Swallowing and Airway Protection

1.2.1 Normal Swallowing

Swallowing is one of the most complex reflexes initiated within the central nervous system (Doty, 1951). It involves the sensory and motor pathways in the cerebrum, cerebellum and brainstem, and numerous muscles innervated by five cranial nerves. To fully understand the disorders of swallowing and their impact, it is essential to first understand both normal swallowing physiology and the mechanisms for protecting the airway from contamination by food, drink and saliva. With each swallow, material is carried from the oral cavity through

the pharynx, past a closed and protected airway, through the oesophagus and then to the stomach in a smooth, continuous and complex series of muscle movements. Various researchers have delineated aspects of swallowing in different ways (Dodds, 1989; Logemann, 1998; Matsuo, 2008), but it is important to acknowledge that these divisions are artificial and events in one phase of swallowing may impact other phases (Daniels & Huckabee, 2014). Daniels and Huckabee (2014) promote a model holistic of swallowing which includes the pre-oral phase, in addition to the oral, pharyngeal and oesophageal phases.

1.2.1.1 Pre-oral Phase

Before food or drink enters the mouth, the body prepares for ingestion in response to stimulation received through the senses. The olfactory nerve (CNI) and occipital nerve (CN II) receive olfactory and visual information and relay this input to the cortex. Salivation is triggered (CN VII, IX) to lubricate the oral cavity and prepare for digestion. Visual and olfactory information from the bolus is processed by the cortex and used to modify the resulting swallowing output (Ebihara et al., 2006; Ushioda et al., 2012).

1.2.1.2 Oral Phase

The start of the oral phase is delineated by bolus entering into the oral cavity. The mouth opens (CN V, AC) and the tongue drops to accept the bolus (CNXII). The bolus is contained anteriorly by the lips (CNVII) and posteriorly by the base of tongue (CN IX & X). Mastication and lingual manipulation (CNV, VII, XII, AC) modify the bolus to a consistency appropriate for swallowing. The base of the tongue drops (CN XII) to allow the bolus access to the pharynx and the tongue presses against the palate (CN XII), anteriorly to posteriorly, to propel the bolus towards the pharynx (Daniels & Huckabee, 2014).

During the pre-oral and oral phases, sensory information is gathered from mechanical and chemical receptors in the teeth (CN V), palate (CN V), mucosa of the mouth and gums (CN V), tongue (V, VII & IX), soft palate (CN IX) and faucial arches (CN X) and is

transmitted via cranial nerves to brainstem (Daniels & Huckabee, 2014; Dodds, 1989). The posterior oral cavity, including the region of the faucial arches and junction of the naso- and oropharynx, is densely innervated with sensory neurons (VII, IX, X). These neurons synapse in the nucleus tractus solitarius (NTS), the primary sensory nucleus for swallowing, located in the dorsal region of the medulla (Miller, 2008; Nishino, 2013). Sensory information from the oral cavity is also relayed to the cortex and is crucial for tailoring the swallowing response to each individual bolus (Miller, 2008; Nishino, 2013; Teismann et al., 2007).

1.2.1.3 Pharyngeal Phase

The swallowing motor plan created in the NTS is transmitted to the nucleus ambiguus (NA), which in turn sends excitatory signals to activate the muscles of the pharynx, larynx and oesophagus (Amri & Car, 1988). The combined contributions of the NTS and NA, and the associated interneurons, constitute a central pattern generator for swallowing (Kessler & Jean, 1985) and are responsible for the pharyngeal response to sensory input in the oral cavity.

Once the brainstem networks initiate the pharyngeal phase, precise timing of events is critical to ensure efficient transfer of the bolus from the upper pharynx to the oesophagus. It is essential that structures of the pharynx are able to move quickly and without obstruction. As the bolus leaves the oral cavity, the soft palate elevates (CN IX, X) to create a closed pressure system in the pharynx (Matsuo, 2008). The base of tongue retracts and the pharyngeal constrictors contract (CN IX & X) to create the beginning of a pressure wave, which moves inferiorly, pushing the bolus towards the oesophagus (Dodds, 1989). More critically, this contraction also shortens and reduces the volume of the pharynx (Matsuo, 2008). The submental muscles pull the hyoid bone anteriorly (CN V, ansa cervicalis), while the posterior belly of the digastric, the stylohyoid and the middle pharyngeal constrictor simultaneously pull it superiorly and posteriorly (CN VII, IX, X) (Ludlow et al., 2007;

Matsuo, 2008). Anterior movement of the hyoid is essential for effective swallowing as it deflects the epiglottis (Steele et al., 2011) and exerts traction on the upper oesophageal sphincter (UES) (Dodds, 1989; Matsuo, 2008). The UES relaxes (CNX) as it is being pulled open and allows passage of the bolus into the oesophagus (Dodds, 1989; Matsuo, 2008).

Several levels of airway protection occur during the pharyngeal phase of swallowing to prevent the bolus from contaminating the airway. The arytenoids approximate (CN X) to bring together the true and false vocal cords (Van Daele, McCulloch, Palmer, & Langmore, 2005), and tilt forward to contact the epiglottis (Matsuo, 2008). The movement of the hyoid, and consequently the thyroid cartilage, positions the larynx underneath the base of the tongue (Matsuo, 2008). The epiglottis, in its deflected position, protects the glottis (Matsuo, 2008). Supraglottic shortening (ansa cervicalis) compresses the quadrangular membrane, blocking the entrance to the laryngeal vestibule (Daniels & Huckabee, 2014). The many levels of airway protection provide redundancy in the case of injury.

Sensory input during the pharyngeal phase is provided by CN IX & X from the oropharynx and hypopharynx and the superior laryngeal nerve (SLN) of the vagus from the larynx and proximal trachea (Armstrong & Netterville, 1995) and recurrent laryngeal nerve (RLN) from the distal trachea. Afferent neurons throughout the pharynx synapse on interneurons within the NTS and directly to the NA in the case of the SLN (Sugiyama et al., 2011), providing sensory information to the brainstem swallowing centres (Miller, 2008). This input allows rapid modulation of the sequence and timing of motor activities during swallowing and generation of prompt airway clearance as needed (Steele & Miller, 2010).

1.2.1.4 Oesophageal Phase

This final phase in the transfer of the bolus from mouth to stomach begins as the bolus passes the UES and enters the oesophagus (Daniels & Huckabee, 2014). As the hyoid descends, the UES passively closes and actively returns to its baseline contracted state. The

muscles of the oesophagus create a peristaltic wave, pushing the bolus to the stomach (Dodds, 1989; Miller, 2008). The innervation of the oesophagus is complex; the smooth muscle of the oesophagus is innervated differently from the striated muscle and both work together in a coordinated fashion to propel the bolus (Miller, 2008). Afferent neurons from the length of the oesophagus synapse in the NTS (Miller, 2008). Sensory input from and motor output to a particular segment of the oesophagus is assigned to a specific region of the NTS (Miller, 2008). This creates a continuous loop of sensory feedback and motor response, allowing the brainstem swallowing centres to tailor the strength of oesophageal contractions to each bolus (Dong, 2001).

Integration of sensorimotor information from numerous central and peripheral neural structures and precise coordination of the movement of several proximal and distal anatomical structures is essential for normal swallowing to occur. Disruption of any part of this process can result in significant swallowing impairment, introducing inefficiency to the swallowing act and compromising swallowing safety.

1.2.2 Airway Protection

The anatomy and physiology of human swallowing is unique from other mammals. As humans have evolved over millions of years, from walking on all fours to standing upright, the larynx has moved further from the oral cavity to its current location near the oesophageal inlet (Brooks, 2011). This has created an increased risk that food, fluid and secretions can be aspirated (Brooks, 2011). The multiple levels of laryngeal closure - closure of the true vocal folds, closure of the ventricular folds, approximation of the arytenoids over the vocal folds, compression of the quadrangular of the membrane and epiglottic deflection - ensure that bolus material does not enter the airway (Daniels & Huckabee, 2014; Matsuo, 2008). However, when laryngeal closure is incomplete due to neurological or structural impairment, a portion of the bolus can enter the laryngeal vestibule and contact the mucosa of

the larynx, trachea or bronchi. The human cough reflex has evolved as the airway's primary defence against the intrusion of foreign material, including airway particles, gastric contents, saliva and ingested food and fluid (Mazzone, Mori, & Canning, 2005).

Cough is defined in the European Respiratory Society (ERS) Guidelines on the Assessment of Cough as “a three-phase expulsive motor act characterized by an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase) and then by opening of the glottis and rapid expiratory airflow (expulsive phase)” (Morice et al., 2007, p. 1256). Each component is essential for an effective cough. Sufficient intake of air during the inspiratory phase and adequate build-up of pressure during the compressive phase result in a powerful expulsive phase, which clears material from the airway, thus preventing aspiration and its potential harmful consequences. The human cough reflex is complex, involving multiple cough receptors responding to different stimuli and, in turn, triggering different types of involuntary cough. This redundancy is seen with other reflexes and has developed over millions of years to protect the airway from aspiration of food, fluid and stomach contents as well as inhalation of irritant chemicals and gasses (Brooks, 2011; Canning & Mori, 2011). Understanding the anatomy and physiology of cough receptors and neural networks is key to understanding the relationship between cough and aspiration.

1.2.3 Airway receptors

The airways are densely lined with a range of receptors designed to detect foreign material. These receptors are identified by the stimuli they respond to and are grouped into mechanoreceptors and chemoreceptors. Each type of receptor triggers a unique motor response; stimulation of more than one receptor type can result in cough. The types of receptors are shown in Figure 1 with characteristics of each receptor outlined.

1.2.3.1 Mechanoreceptors

Lung inflation, bronchospasm and light touch, such as that created by a piece of aspirated food or liquid, all trigger low threshold mechanoreceptors (Canning, 2006; Mazzone, 2005). In addition, some chemicals can indirectly trigger mechanoreceptors, including citric acid. This is thought to be because their contact with the mucosa triggers bronchospasm and mucous secretions, which in turn activate the rapidly adapting receptors (RAR) (Canning, 2006; Mazzone, 2005). The best-known types of mechanoreceptors, RARs and slowly adapting receptors (SARs), share many characteristics, such as their origination and termination points, action potential range and response to mechanical stimuli. However, there are differences that make these two receptor types distinct (Mazzone, 2005).

RARs are present primarily in the intrapulmonary airways, although they do exist throughout the airways (Canning, 2006). RARs are so called because they quickly adapt to sustained stimulus, as in the case of a breath-hold (Canning, 2006). RARs are active throughout the inflation and deflation of the lungs and become increasingly active when rate and volume of breathing increases (Canning, 2006). When stimulated, rapid breathing ensues, the smooth muscles of the airway contract and mucous production increases (Canning, 2006; Mazzone, 2005). Many stimuli that activate RARs do not activate cough and stimuli that induce cough through stimulation of RARs do so only under specific conditions. This suggests that stimulating cough is not the primary role of the RARs (Canning, 2006).

SARs are most active at peak lung inflation and are likely involved in ceasing inspiration and initiating expiration. They also have a role in airway tone (Mazzone, 2005). SARs appear to play a role in cough, possibly modulating the expiratory effort in cough, although cough stimulation does not appear to be their primary function (Canning, 2006).

Properties	RARs	SARs	C-Fibers
Electrophysiologic			
Conduction velocity, m/s	14–23	15–32	0.8–1.5
Myelination	Yes	Yes	No
Eupneic activity, impulses/s	0–20	10–40	0.3–1.5
Morphologic			
Neuropeptide synthesis	No	No	Yes
Innervation of large airways†	Yes	Sparse	Yes
Innervation of small airways	Yes	Yes	Yes
Physical sensitivity			
Mechanical threshold	Low	Low	High
Lung deflation*	Activated	Inactivated	No effect
Edema	Increased	No effect	Increased
Chemical sensitivity*			
CO ₂	No effect	Decreased	Increased
H ⁺	Increased	No effect	Increased
Capsaicin*	Increased†	No effect	Increased‡
Bradykinin*	Increased†	No effect	Increased‡
Reflex effects			
Parasympathetic	Excitatory	Inhibitory	Excitatory
Respiratory	Hyperpnea	Inhibit inspiration	Apnea
Axon reflex	No	No	Yes

*Typical attributes of the afferent nerve subtypes are listed. Species differences and subtypes of each class with distinct physiologic properties and responsiveness have been reported.

†The activation of RARs by capsaicin and bradykinin is prevented by bronchodilator pretreatment, suggesting that activation occurs secondary to obstruction in the lung.

‡C-fiber activation by bradykinin and capsaicin is enhanced by bronchodilators such as adrenaline, adenosine, and prostaglandin E, suggesting that agents directly stimulate C-fibers in the airways. See text for further details and references.

Figure 1. Properties of Airway Receptors.

From “Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines,” by B. J. Canning, 2006, *Chest*, 129, p. 33S to 47S. Copyright 2006 by American College of Chest Physicians. Reprinted with permission.

1.2.3.2 Chemoreceptors

In contrast to RARs and SARs, chemoreceptors are not active during normal breathing. Chemoreceptors become active when the airways are irritated or inflamed, and can be stimulated by exposure to a variety of chemicals, including capsaicin, bradykinin, citric acid and sulphur dioxide (Canning, 2006; Mazzone, 2005). Chemoreceptors are located throughout the airways. Some of these receptors can also be triggered with a very strong mechanical stimulation, such as the prodding of the laryngeal mucosa (Canning, 2006; Mazzone, 2005).

C-fibers are the most common type of chemoreceptor and the most prevalent receptor innervating the airways and lungs. They are unmyelinated, in contrast to RARs and SARs, and conduct signals at a lower velocity. Stimulation of C-fibers provokes apnoea, bradycardia, hypotension and, in guinea pigs and rats, bronchospasm, mucous secretion and neurogenic inflammation (Canning, 2006; Lee & Undem, 2008). C-fiber activation may provoke cough, as the chemical stimulants that activate C-fibers can trigger coughing in conscious humans and animals (Canning, 2006; Lee & Undem, 2008). In particular, stimulation with bradykinin and capsaicin result in paroxysmal coughing (Canning & Mori, 2011). C-fiber activation in anaesthetised animals does not trigger cough (Canning & Mori, 2011). In addition, coughing in humans in response to capsaicin is always preceded by a reported irritation in the throat, termed an “urge to cough” (Davenport, Sapienza, & Bolser, 2002; Mazzone, McGovern, Koo, & Farrell, 2009; Mazzone, McLennan, McGovern, Egan, & Farrell, 2007). For these reasons, C-fiber-triggered cough is thought to involve sensory processing and be, at least in part, a behavioural response to airway irritation, not a pure reflex (Lee & Undem, 2008; Mazzone et al., 2009). C-fibers are not likely to be the primary cough receptor, but do clearly play an important role in cough (Canning, 2006).

1.2.3.3 True Cough Receptors

A group of receptors, present in the larynx, trachea and, to a lesser extent, main stem bronchi, which respond to both mechanical and chemical stimuli, have been termed the “true” cough receptors (Canning, 2006; Mazzone, 2005). Canning first identified what he termed the “true” cough receptor in guinea pigs, but he suggests they also exist in humans (Canning, 2006). These receptors are myelinated and are known to be incredibly sensitive to punctuate stimuli as well as acid, water and 4-aminopyridine, but do not respond to capsaicin, hypertonic saline solution or bradykinin (Canning, 2006; Canning & Mori, 2011). True cough receptors are similar to RARs in myelination and that they adapt to stimuli (Canning, 2006; Lee & Udem, 2008), but are distinguished from other mechanoreceptors by their sensitivity to unique stimuli and slower action potential than RARs and SARs (Canning, 2006; Lee & Udem, 2008). Stimulation of the true cough receptor triggers a few powerful coughs, which would be effective for clearing aspirated material (Canning & Mori, 2011). In addition, their sensitivity to acid, including citric acid, and subtle mechanical stimuli may point to their role in protecting the airway from aspiration of foreign matter, including food, fluid and stomach contents (Brooks, 2011; Morice et al., 2007).

1.2.4 Afferent Pathways of Cough

Whether cough is triggered by a chemical or mechanical stimulus, transduction of the signal to the brain begins with an interaction between the stimulus and the molecules of the nerve terminals. When the threshold is reached an action potential is triggered and travels via the vagus nerve to the brainstem (Kollarik & Udem, 2006). The signal travels primarily ipsilaterally, but both branches of the vagus nerve transduce signals from the receptors to the brainstem, such that damage to one of the vagus nerves will not impact cough (Canning, 2006). Both the RLN and SLN branches of the vagus nerve contain afferent nerves from the airway receptors (Canning et al., 2004). The RLN plays a greater role in cough. When the

RLNs of anaesthetised guinea pigs were severed bilaterally, stimulation to the larynx and trachea did not trigger cough, but severance of the SLNs had no effect (Canning et al., 2004).

The afferent fibres of the vagal nerves continue via the nodose and jugular ganglia to the brainstem where they terminate primarily at the NTS, a complex integration centre of afferent input located in the medulla, within the brainstem (Narula, McGovern, Yang, Farrell, & Mazzone, 2014). In response to mechanical stimulation or acid inhalation, presumably stimulating the true cough receptor, a purely reflexive cough can be triggered via neural projections from the NTS to the ventral respiratory group (Narula et al., 2014; Shannon et al., 2004). This brainstem reflex is not cortically controlled and cannot be consciously modified. Triggering of the reflex results in an extremely rapid cough motor output, likely intended to protect the airways from aspiration (Ando, Farrell, & Mazzone, 2014; Canning & Mori, 2011).

In the case of cortically modulated cough, the pathway to the brainstem is shared. The action potential travels via the vagus nerve to the NTS and connects with second order neurons, which transmit the signal to supramedullary areas (Mazzone et al., 2009). Functional magnetic resonance imaging during inhaled capsaicin challenges has revealed numerous areas of the brain activated with urge-to-cough including the sensorimotor cortex, anterior mid-cingulate cortex, anterior insula, prefrontal cortex supplementary motor area, cerebellum, thalamus and lentiform nuclei (Farrell, Cole, Chiapoco, Egan, & Mazzone, 2012; Mazzone et al., 2009; Mazzone et al., 2007). Some areas of the brain appear to be involved in localising the irritating sensation (Farrell et al., 2012). Other areas, which show dose-dependent responses, process the sensory information while yet others may be involved in suppressing cough (Farrell et al., 2012). The purpose of the urge to cough is presumably to engage the cortex in evaluating the cough and modifying the cough response. Precisely how this occurs is not fully understood (Davenport, Vovk, Duke, Bolser, & Robertson, 2009).

However, it is important to acknowledge the ability of humans to exercise wide-ranging control over cough output, including the production of a purely volitional cough, suppressing the urge to cough and coughing in response to placebo stimuli (Ando et al., 2014). These factors can all make assessment of cough very challenging.

1.2.5 Other airway reflexes

The cough reflex exists alongside other airway protection reflexes, which assist in keeping the airways clear of harmful material. The expiratory reflex and glottic closure reflex can be triggered by stimulation to the vocal cords or mucosa of the trachea (Widdicombe, Eccles, & Fontana, 2006). The expiratory reflex, which is defined as immediate closure and reopening of the glottis that coincides with exhalation, without preceding inhalation, may occur prior to a reflexive cough (Fontana & Lavorini, 2006; Widdicombe, Addington, Fontana, & Stephens, 2011). The purpose of the expiratory reflex is presumably to assist with clearance of material from the airway prior to cough and plays an important role in clearing aspirate from the airway (Fontana & Lavorini, 2006; Widdicombe et al., 2011). An individual response to aspiration may consist of several expiratory reflexes, coughs and glottal closures in rapid succession, referred to as a cough epoch (Widdicombe et al., 2006). Although assessment of airway protection in patients who are at risk of aspiration has focused on the cough reflex, these other reflexes likely also play an important role in preventing aspiration or clearing material from the airway after it has been aspirated.

1.2.6 Motor Component of Coughing

The efferent pathways of the brainstem are not unique to cough. The pathways and brainstem structures that produce coughing are the same that produce tidal breathing as well as other reflexes, including swallowing, expiration reflex, gagging, laryngospasm, bronchoconstriction, apnoea and retching (Brooks, 2011; Mazzone, Cole, Ando, Egan, & Farrell, 2011; Shannon et al., 2004). In the case of purely reflexive cough, the action potential

is conveyed from the airway receptors to the NTS in the medulla as described above. From there, interneurons conduct the signal to the pontine and ventral respiratory groups and further through a complex brainstem network that is not fully understood (Shannon et al., 2004). The usual breathing pattern is reconfigured to produce a cough pattern and the pre-motor drive is conducted to the respiratory and motor neuron pools (Mazzone et al., 2011; Narula et al., 2014; Shannon et al., 2004). In the case of urge-related coughing, corticobulbar tracks from the motor control centre provide further input to the brainstem cough centres to suppress or modify cough output (Mazzone et al., 2011). Interestingly, voluntary cough appears to bypass the medulla, utilising a corticospinal tract (Mazzone et al., 2011). The entire afferent and efferent pathway is pictured in Figure 2.

1.2.7 Summary

Swallowing has been described as a four-phase process, consisting of the pre-oral, oral, pharyngeal and oesophageal phases. It is a complex process that requires integration of sensory input and motor output as well as the precise and rapid movement of a number of structures. When this process is disrupted and laryngeal closure is incomplete, bolus may enter the airway. The cough reflex has evolved alongside other airway reflexes to protect the airway from contamination.

Cough occurs in response to the stimulation of mechano- and chemoreceptors in the airways. The signal from the receptors is conveyed via the vagus nerve to the brainstem and, in the case of cortically modulated cough, to the cortex via second order neurons. Centres in the brainstem reconfigure the normal respiratory pattern in response to sensory input to produce the three phases of cough: inspiratory, compressive and expulsive. Knowledge of the various airway receptors, including mechano- and chemoreceptors, and their sensitivity to various tussigens is essential for understanding CRT methodology.

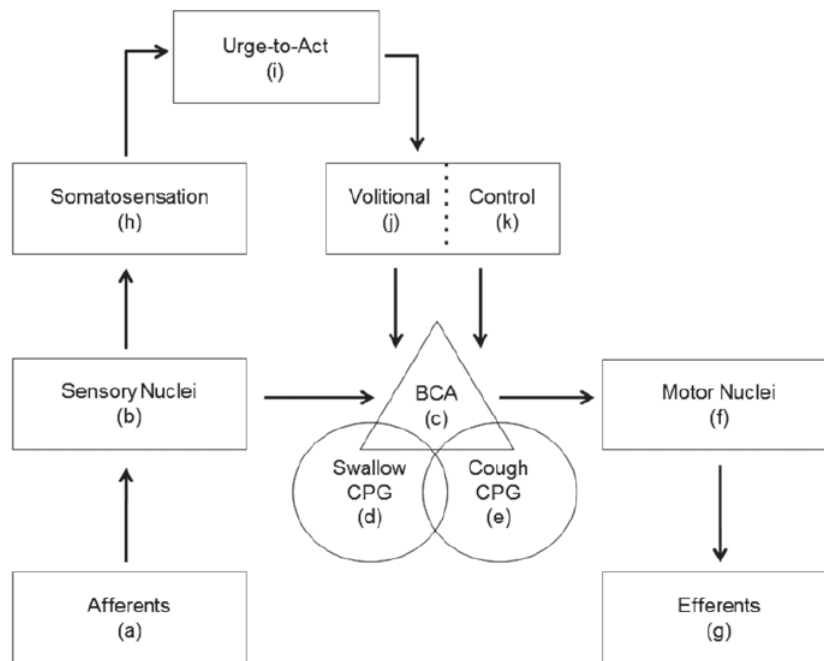


Figure 2- Proposed framework of airway protection. Cough and swallowing share afferents (a) that are essential to the initiation and modification of the behaviors. This afferent (a) information is then sent to the sensory nuclei (b) located in the brainstem. There, the behavioral control assembly (BCA) (c) will receive the afferent information and exert control over the swallowing and cough central pattern generators (CPGs) (d & e) in order to generate the appropriate airway protective behavior. Information fed into the motor nuclei (f) is then sent to the efferent (g) nerves. Information from the brainstem sensory nuclei (b) travels through ascending pathways to the cortex via the thalamus, allowing for somatosensation (h) of the stimulus. Preceding the motor output there is an urge to act (i) on the stimulus. This will enable suppression or up-regulation of the airway protective behavior through volitional control (j). Both cough and swallowing can be initiated through volitional control (k), or on command. This neural information then travels through descending pathways to the brainstem and then through efferents (g) to the periphery

Figure 2. Revised Model for the Neural Control of Cough.

From “A framework for understanding shared substrates of airway protection,” by M. S. Troche, A. E. Brandimore, J. Godoy, & K/ W. Hegland, 2014, *Journal of Applied Oral Science*, 22(4), p. 251-260. Open Access by SciELO 2014.

1.3 ***Disordered Swallowing***

Dysphagia is the term used to describe a disruption in the normal process of swallowing. Dysphagia can occur during any of the phases of swallowing and can result from any condition that impacts the structure or function of swallowing. For the purposes of this discussion, the term dysphagia will be narrowly defined, referring exclusively to oropharyngeal dysphagia. In a 2012 household survey of Americans, 4% of the adult population reported experiencing dysphagia within the previous 12 months (Bhattacharyya,

2014). Bhattacharyya (2014) grouped the causes of dysphagia into several categories: stroke, neurologic disease, head and neck cancer, advanced age, injury to the head or neck, prescription medication or drugs, congestive heart failure, arthritis or chronic obstructive pulmonary disease. Over 11% of respondents attributed their dysphagia to a stroke and another 7.2% attributed it to another neurological cause, such as Alzheimer's, Parkinson's or Multiple Sclerosis, making neurological diagnoses by far the most common cause of dysphagia among the survey respondents. Indeed, stroke (Mann, Hankey, & Cameron, 2000) and Parkinson's disease (Kalf, De Swart, Bloem, & Munneke, 2012) are well recognised as causing impaired function of swallowing. Neurological causes of dysphagia may be common, but with only 18% of respondents attributing their dysphagia to neurological impairment, it is apparent that the causes of dysphagia are varied. Head and neck cancer (4.9%), advanced age (2.6%) and head or neck injury (2.6%) were the third, fourth and fifth most commonly identified causes of dysphagia. Notably, 70% of respondents identified a cause that could not be easily categorised, again reflecting the vast and varied causes of dysphagia.

Dysphagia can occur at any age, but is more common in elderly individuals than in younger, with Bhattacharyya (2014) reporting an increased odds ratio of 1.19 per decade of life. Dysphagia is particularly prevalent in adults over 85 years of age (Bhattacharyya, 2014) and in elderly residents of residential care (Easterling & Robbins, 2008; Park et al., 2013). It is also common in the hospital setting as both an acute and a chronic health issue. For example, an elderly patient with a longstanding dysphagia may be admitted for treatment of pneumonia, or may develop dysphagia suddenly as a result of an acute illness that requires hospitalisation (Pizzorni et al., 2014). Cichero, Heaton and Bassett (2009) screened patients admitted to medical wards over a seven week period and reported a dysphagia prevalence of 25%. ICUs treat the most critically ill hospitalised patients and dysphagia is common in this patient cohort (Macht, Wimbish, Bodine, & Moss, 2013). ICU patients may have a range of

factors related to their primary illness, co-morbidities or as a side effect of treatment that could contribute to the occurrence of dysphagia. Very often dysphagia will result from a combination of several factors. Potential mechanisms for dysphagia in ICU patients have been categorised by Macht and colleagues (2013) and are listed in the Figure 3.

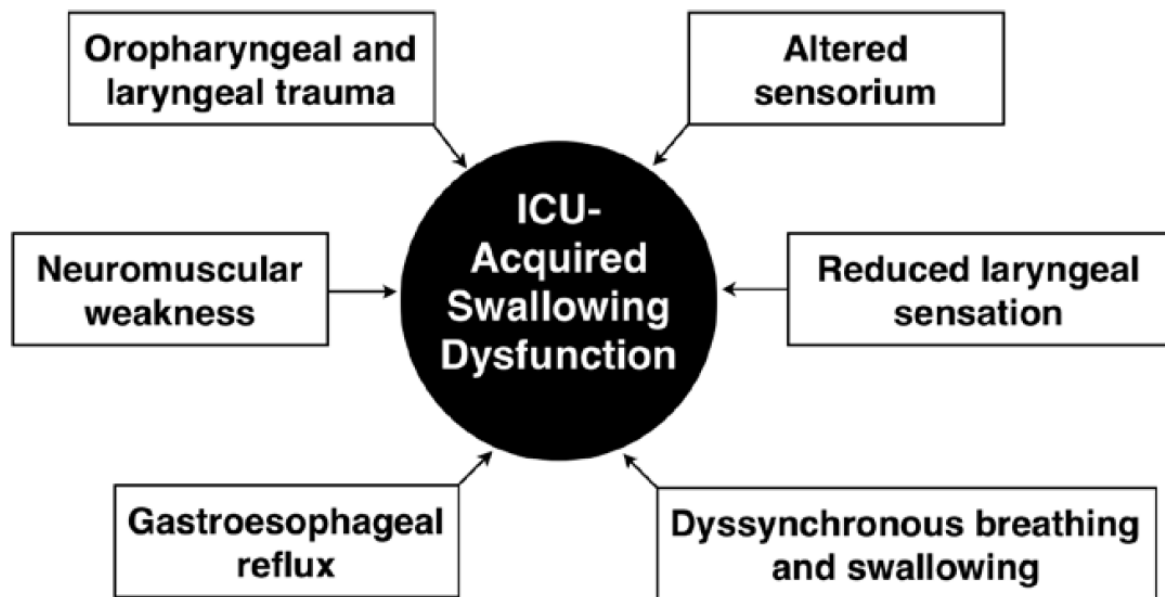


Figure 3. Six Potential Mechanisms for the Development of ICU-Acquired Swallowing Disorders.

From “ICU-acquired swallowing disorders,” by Macht, Wimbish, Bodine, & Moss, 2013, *Critical Care Medicine*, 41(10), p. 2396-2405. Copyright 2013 by Wolters Kluwer Health, Inc.. Reprinted with permission.

1.3.1 Consequences of Dysphagia

Individuals with dysphagia can experience a number of serious consequences. One potential consequence of dysphagia is aspiration. When swallowing is impaired, it is possible for the bolus, or a portion of the bolus, to contaminate the larynx. Aspiration occurs when ingested material penetrates the upper airway to the point of contacting the vocal folds. A

cough should be triggered at this point to clear the aspirated material from the larynx (Pitts et al., 2013). However, ‘silent’ aspiration occurs when material enters the airway and contacts or passes below the vocal folds without stimulating an overt, behavioural response. Aspiration, both overt and silent, is a well-documented issue in the ICU population (Ajemian et al., 2001; El Solh et al., 2003; Leder et al., 1998; Macht et al., 2013; Scheel et al., 2016) and has serious consequences.

1.3.1.1 Pneumonia

Critically ill patients with dysphagia are more likely to have poor outcomes than their counterparts without dysphagia (Macht et al., 2011). Macht and colleagues (2011) reviewed the medical records of 630 ICU patients who were referred to SLT after extubation. The presence of dysphagia, as identified by clinical assessment, was significantly and independently associated with pneumonia, reintubation and death. This finding is likely due in part to the link between aspiration and pneumonia.

When aspiration occurs as a result of dysphagia, oropharyngeal material colonised with pathogenic bacteria from the oral cavity may enter the lungs. This triggers an acute pulmonary inflammatory response, known as aspiration pneumonia (Marik, 2001). Aspiration is a key precursor to aspiration pneumonia, but aspiration itself does not always lead to pneumonia. In an important study by Langmore, Terpenning, Schork, Chen, Murray and colleagues (1998), the authors identified several key risk factors that contributed to the development of pneumonia in a cohort of male veterans with a range of medical conditions across the outpatient, inpatient acute and residential care settings. The authors reported that pneumonia is most likely to develop when there is bacterial colonisation, an aspiration event and reduced host resistance. The specific factors that correlated with development of pneumonia are outlined in the Figure 4. It is important to note that the study did not include ICU patients. Therefore, translation of these identified risks may not directly apply to patients

who are critically unwell, but it is worth considering the findings of this study in the ICU context as many patients present with a number of the factors identified by Langmore and colleagues (1998).

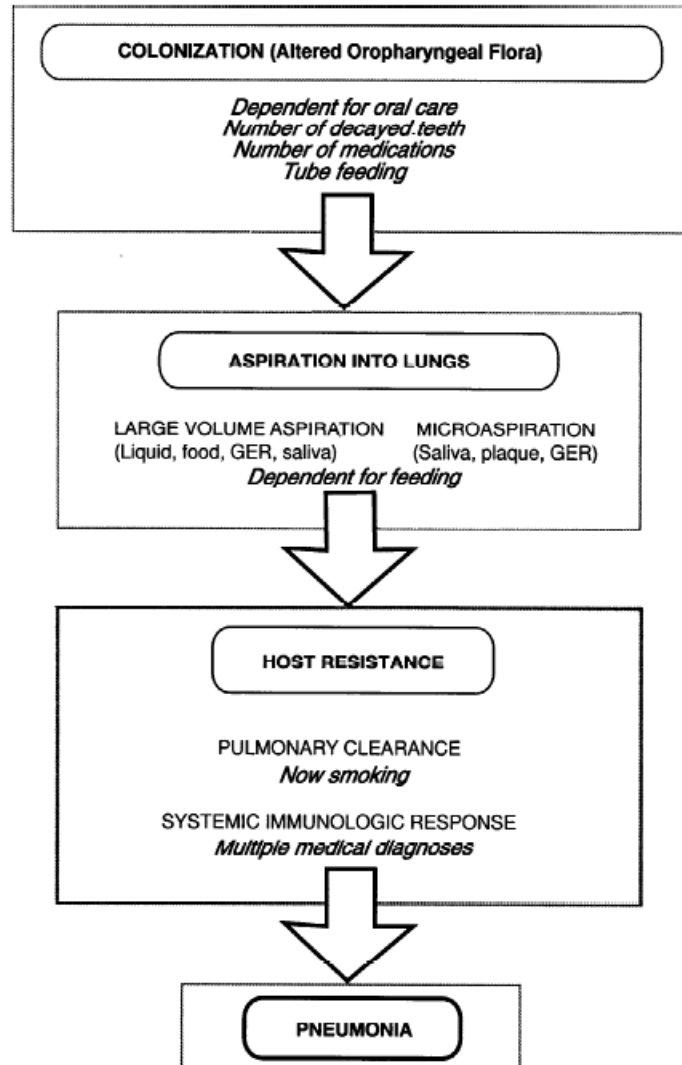


Figure 4. Significant Predictors of Aspiration Pneumonia.

From “Predictors of aspiration pneumonia: how important is dysphagia,” by S. E. Langmore, et al., 1998, *Dysphagia*, 13(2), p. 69-81. Copyright 1998 by Springer. Reprinted with permission.

Pneumonia in the ICU population can be loosely grouped into two categories: community-acquired and hospital acquired, which is known as nosocomial pneumonia

(Herkel et al., 2016). Patients may be admitted to ICU with a community-acquired pneumonia, but when the pneumonia presents during ICU treatment it is considered nosocomial pneumonia. Critically ill patients are at high risk of nosocomial pneumonia due to several risk factors inherent to this population, including supine positioning and the prevalence of gastroparesis, nasogastric feeding and gastroesophageal reflux (Drakulovic et al., 1999; Kollef, 1993; Marik, 2001; Potts, Zaroukian, Guerrero, & Baker, 1993). When nosocomial pneumonia occurs within 48 hours of mechanical ventilation it is termed ventilator associated pneumonia (VAP) (Hunter, 2006). VAP is the most common nosocomial infection in ICU. A survey of relevant literature on VAP revealed that 10% to 20% of patients who were ventilated for more than 48 hours developed VAP (Hunter, 2006). Development of VAP can have significant consequences on an individual's hospital course and outcome. In a study by Safdar, Dezfulian, Collard and Saint (2005), mean ICU length of stay for patients who developed pneumonia was 6.1 days longer than their counterparts without pneumonia. When calculated into United States dollars in 2005, this equated to over \$10,000 per stay in additional cost. In addition, the odds ratio for death in ICU was 2.03 for patients with pneumonia when compared to patients without pneumonia.

Aspiration is a major contributor to VAP as ventilated patients usually do not have the ability to protect their airway and the endotracheal tube can act as a conduit for pathogens to travel from the mouth to the lungs (Bouza et al., 2003; Bouza et al., 2008; Safdar et al., 2005). Chevret, Hemmer, Carlet and Langer (1993) followed 996 patients from ICU admission to hospital discharge and reported that impaired airway reflexes at the time of ICU admission were the best predictor of nosocomial pneumonia. The authors defined decreased airway reflexes as “severe impairment of spontaneous breathing, glottic closure and cough reflexes with reduced defence reactions to endotracheal intubation or pharyngeal suctioning” (Chevret et al., 1993, p.257). Patients with decreased airway reflexes were 2.3 times more

likely to develop pneumonia during their admission. Twenty-two percent of patients who required greater than 48 hours of intubation developed pneumonia compared to 9% of all patients admitted to ICU. These results strongly suggest that strategies that could reduce the occurrence of aspiration in this population would be beneficial for patient outcomes.

1.3.1.2 Malnutrition

When individuals have difficulty eating and drinking their caloric consumption is reduced. ICU patients who are started on an oral diet soon after extubation manage approximately half of their daily nutritional requirements in the week following extubation due to a range of factors, including restricted diets, lack of appetite, nausea and vomiting (Peterson et al., 2010). Because patients with moderate to severe dysphagia are significantly more likely to have a delay in resuming oral intake after extubation (Barker, Martino, Reichardt, Hickey, & Ralph-Edwards, 2009), this population is particularly at risk of malnutrition. The link between dysphagia and malnutrition is well established (Hudson, Daubert, & Mills, 2000). Malnutrition puts individuals at increased risk of mortality and morbidity. Morbidities include loss of muscle function, cardio-respiratory function and gastrointestinal function as well as reduced immunity, wound healing and psychosocial well-being (Saunders & Smith, 2010). In already unwell ICU patients, malnutrition is significantly and adversely associated with mortality, length of stay and cost of treatment (Lew et al., 2016).

1.3.1.3 Cost of treatment

The presence of dysphagia after orotracheal intubation is widely recognised to increase length of stay (Barker et al., 2009; Bordon et al., 2011; Brown et al., 2011; Ferraris, Ferraris, Moritz, & Welch, 2001; Hogue et al., 1995; Macht et al., 2011; Rousou et al., 2000). In a mixed ICU population without neurological deficits who had mechanical ventilation for any time period, median length of ICU stay was 3 days for patients without dysphagia

compared to 10 days for patients with dysphagia (Macht et al., 2011). This finding was supported by a study evaluating post-extubation dysphagia in a group of patients following cardiac surgery (Ferraris et al., 2001). Patients without oropharyngeal dysphagia required a significantly shorter length of post-operative stay ($M = 5.7$ days) than patients with oropharyngeal dysphagia ($M = 16.1$ days). This complication has not only medical but financial implications. The increased length of hospital stay in the study by Ferraris and colleagues (2001) translated to an average cost of treatment of US\$36,087 for non-dysphagic patients versus US\$69,320 for those with dysphagia.

1.3.2 Causes of Dysphagia in ICU

An audit of ICU admissions was completed in 2005 for 91 hospitals that contribute to the United Kingdom Trauma Audit and Research Network (Simpson, Clancy, Goldfrad, & Rowan, 2005). The main aim of the audit was to identify characteristics of patients admitted to ICU directly from the emergency department (ED); however, the researchers included data for all 46,587 admissions to ICUs that occurred between 1996-1999, categorised into ED admissions and non-ED admissions (Figure 5). Each individual ICU is likely to have its own unique case mix and the study by Simpson and colleagues (2005) provides a very broad picture of the wide variety of patients admitted to ICU, which will be more or less representative of an individual ICU.

Macht and colleagues' six mechanisms of dysphagia (2013) provide a useful framework for considering the effect of each diagnosis on swallowing. When the data from Simpson and colleagues (2005) and the six mechanisms of dysphagia (Macht et al., 2013) are considered together, it is possible to hypothesize the profile of dysphagia in an ICU. The list of diagnoses provided in Simpson and colleagues' survey (2005) is extensive and considering the potential impact of each on swallowing is outside the scope of this thesis, but it is worth considering a few aetiologies that are commonly linked to swallowing disorders.

Table 2 Reason for admission of admissions to intensive care units (ICUs) from emergency departments (EDs)

Direct admissions to ICU from EDs (n=9389)			Indirect admissions to ICU from EDs (n=2879)			Non-ED ICU admissions (n=34 319)		
Patient category	n	%	Patient category	n	%	Patient category	n	%
Poison (accidental and non-accidental)	1261	13.4	Respiratory—pneumonia and respiratory tract infections	497	17.3	Surgery (non-trauma)—gastrointestinal tract	5075	14.8
Trauma—head and face	1163	12.4	Cardiac—circulatory collapse/shock	438	15.2	Surgery (non-trauma)—vascular	4343	12.7
Cardiac—ischæmic heart disease	799	8.5	Respiratory—asthma and chronic lung disease	281	9.8	Cardiac—circulatory collapse/shock	3486	10.2
Cardiac—circulatory collapse/shock	703	7.5	Poison (accidental and non-accidental)	149	5.2	Respiratory—pneumonia and respiratory tract infections	2293	6.7
Surgery (non-trauma)—neurosurgery	582	6.2	Surgery (non-trauma)—hepatobiliary and pancreas	134	4.7	Surgery (non-trauma)—chest	1680	4.9
Respiratory—asthma and chronic lung disease	547	5.8	Cardiac—ischæmic heart disease	131	4.6	Cardiac—ischæmic heart disease	1292	3.8
Surgery (non-trauma)—vascular	502	5.4	Surgery (non-trauma)—GI tract	130	4.5	Surgery (non-trauma)—hepatobiliary and pancreas	1239	3.6
Trauma—orthopaedic and spinal	430	4.6	Cardiac—arrhythmia	119	4.1	Respiratory—asthma and chronic lung disease	1130	3.3
Trauma—chest	410	4.4	Trauma—chest	95	3.3	Respiratory—airway problems	1101	3.2
Cardiac—arrhythmia	409	4.4	CNS—fits	89	3.1	Anaesthetic reasons and complications	1045	3.0
Trauma—abdomen	352	3.8	Medical—renal failure	82	2.9	Surgery (non-trauma)—renal or urogenital	1004	2.9
Respiratory—pneumonia and respiratory tract infections	335	3.6	Surgery (non-trauma)—neurosurgery	75	2.6	Surgery (non-trauma)—neurosurgery	864	2.5
CNS—fits	290	3.1	Medical—biochemical/endocrine/metabolic derangement	61	2.1	Cardiac—arrhythmia	862	2.2
Surgery (non-trauma)—gastrointestinal tract	285	3.0	Respiratory—other	58	2.0	Respiratory—other	859	2.5
CNS—coma, other cause	253	2.7	CNS—infection	54	1.9	Trauma—head and face	776	2.3
CNS—infection	148	1.6	Respiratory—aspiration/inhalation injury	53	1.8	Surgery (non-trauma)—orthopaedic/spinal/rheumatology	625	1.8
Respiratory—airway problems	147	1.6	Medical—other conditions	48	1.7	Medical—renal failure	589	1.7
Medical—biochemical/endocrine/metabolic derangement	139	1.5	Trauma—head and face	48	1.7	Surgery (non-trauma)—other abdominal	574	1.7
Respiratory—aspiration/inhalation injury	137	1.5	CNS—coma, other cause	43	1.5	Cardiac—other	511	1.5
Respiratory—other	67	0.7	Surgery (non-trauma)—chest	42	1.5	Medical—other conditions	445	1.3
Surgery (non-trauma)—chest	61	0.7	Cardiac—other	40	1.4	Trauma—orthopaedic and spinal	437	1.3
Trauma—burn and dermal injury	38	0.4	Respiratory—acute respiratory distress syndrome	26	0.9	Poison (accidental and non-accidental)	416	1.2
Medical—other conditions	37	0.4	Trauma—orthopaedic and spinal	24	0.8	Respiratory—aspiration/inhalation injury	416	1.2
Cardiac—other	35	0.4	Respiratory—airway problems	23	0.8	Trauma—abdomen	413	1.2
Hypothermia and hyperthermia (accidental)	34	0.4	Medical—neuromuscular disorder	22	0.8	Surgery (non-trauma)—obstetrics and gynaecology	350	1.0
Surgery (non-trauma)—hepatobiliary and pancreas	34	0.4	Surgery (non-trauma)—vascular	21	0.7	Medical—biochemical/endocrine/metabolic derangement	327	1.0
Medical—renal failure	32	0.3	Surgery (non-trauma)—renal or urogenital	18	0.6	CNS—fits	308	0.9
Surgery (non-trauma)—other abdominal	30	0.3	Surgery (non-trauma)—other abdominal	17	0.6	Trauma—chest	295	0.9
Anaesthetic reasons and complications	25	0.3	Trauma—abdomen	10	0.4	Respiratory—acute respiratory distress syndrome	278	0.8
Uncoded	18	0.2	Unclassifiable	9	0.3	CNS—infection	274	0.8
Respiratory—acute respiratory distress syndrome	15	0.2	Uncoded	9	0.3	Surgery (non-trauma)—maxillofacial/ENT/ophthalmology	270	0.8
Medical—neuromuscular disorder	14	0.2	Anaesthetic reasons and complications	8	0.3	CNS—coma, other cause	250	0.7
Surgery (non-trauma) orthopaedic/spinal/rheumatology	14	0.2	Hypothermia and hyperthermia (accidental)	7	0.2	Medical—neuromuscular disorder	214	0.6
Surgery (non-trauma)—renal or urogenital	12	0.1	Surgery (non-trauma)—maxillofacial/ENT/ophthalmology	6	0.2	Unclassifiable	96	0.3
Surgery (non-trauma)—maxillofacial/ENT/ophthalmology	10	0.1	Surgery (non-trauma)—orthopaedic/spinal/rheumatology	6	0.2	Uncoded	80	0.2
Surgery (non-trauma)—obstetrics and gynaecology	10	0.1	CNS—other	3	0.1	Trauma—burn and dermal injury	58	0.2
Unclassifiable	5	0.1	Surgery (non-trauma)—obstetrics and gynaecology	2	0.1	Surgery (non-trauma)—other	23	0.1
CNS—other	4	0.0	Trauma—burn and dermal injury	1	0.0	Hypothermia and hyperthermia (accidental)	10	0.0
Medical—psychiatric/other confusional state	1	0.0	Medical—psychiatric/other confusional state	0	0.0	CNS—other	9	0.0
Surgery (non-trauma)—other	1	0.0	Surgery (non-trauma)—other	0	0.0	Medical—psychiatric/other confusional state	2	0.0

Figure 5. Reason for Admission to ICUs from EDs.

From “Admissions to intensive care units from emergency departments: a descriptive study,” by H. K. Simpson, M. Clancy, C. Goldfrad & K. Rowan, 2005, *Admissions to intensive care units from emergency departments: a descriptive study*, *Emergency Medicine Journal*, 22(6), p. 423-428. Copyright 2005 by BMJ Publishing Group, Ltd.. Reprinted with permission.

1.3.2.1 Neurological Causes of Dysphagia in ICU

Macht and colleagues' (2013) six mechanisms of dysphagia are highly relevant to ICU patients with neuromuscular disorders. This population may experience dysphagia that occurs through four of the six mechanisms: weakness (Robbins et al., 2007), reduced laryngeal sensation (Stephens, Addington, & Widdicombe, 2003), altered sensorium (Ji et al., 2013), and dyssynchronous breathing and swallowing (Wang, Shieh, Chen, & Wu, 2015). Patients with severe neurological injury may also be bedbound for an extended period of time, placing them at risk of gastroesophageal reflux (Aderinto - Adike & Quigley, 2014), which adds an additional potential mechanism of dysphagia. Patients with neuromuscular disorders may require admission to ICU. Indeed, in their audit of ICU admissions, Simpson and colleagues (2005) reported almost 3500 admissions (7.5%) for central nervous system disorders, neuromuscular disorders and conditions requiring neurosurgery. This category encompasses a wide range of diagnoses, including ischaemic and haemorrhagic strokes, head injury, seizures, progressive neurological disorders and brain tumours.

Each of these aetiologies presents a unique profile of risk, with some patients at greater risk of dysphagia than others. Stroke patients are at particularly high risk of dysphagia, with the prevalence reported to be as high as 64% following stroke (Mann et al., 2000). A similar prevalence has been reported following head injury. Mackay, Morgan and Bernstein (1999) performed videofluoroscopic swallowing studies (VFSS) on 54 consecutively enrolled patients with severe head injury and reported an incidence of dysphagia of 61%. Although Simpson and colleagues (2005) do not specifically report the number of patients admitted with head injury, they did record 1,987 (4.3%) admissions for trauma to the head and neck. Other researchers have estimated that approximately 3,500 patients are admitted to ICU with head injury each year in the United Kingdom (Helmy,

Vizcaychipi, & Gupta, 2007), indicating that dysphagia resulting from head injury is a significant issue in ICU.

Patients admitted with any primary diagnosis that requires prolonged ICU admission may develop systemic weakness over the course of their treatment, which can be classified as critical illness polyneuropathy (CIP) (Apostolakis, Papakonstantinou, Baikoussis, & Papadopoulos, 2015). CIP has been defined as “a predominantly motor, axonal dysfunction of unknown aetiology, with acute onset after development of respiratory insufficiency in a setting of systemic inflammatory response with multiple organ dysfunction” (Leijten & De Weerd, 1994, p. 15). In a prospective study of 22 patients with CIP who underwent videoendoscopy (VES) during admission to a neurological rehabilitation ICU, disordered swallowing was identified in 20 (91%) participants (Ponfick, Linden, & Nowak, 2015). More specifically, 13 of 17 (78%) participants who were offered thin liquids aspirated on VES performed on the third day of admission to the unit.

Collectively, the above figures above represent just a portion of patients with neurological impairment admitted in ICU, but do provide some insight into the significance of neurological dysphagia in the ICU patient cohort. The combination of swallowing impairment with concomitant risk factors present in the critically ill ICU population may make ICU patients with neurological injury particularly susceptible to aspiration and subsequent development of nosocomial pneumonia.

1.3.2.2 Dysphagia following surgery

Simpson and colleagues (2005) reported that nearly 40% of ICU admissions were related to surgical management. ICU patients may experience dysphagia as a consequence of surgical management for a number of reasons, one being perioperative stroke (Selim, 2007). Risk of perioperative stroke depends on the complexity and type of surgery. For example, duration of cardiopulmonary bypass and cross-clamp time are risk factors for perioperative

stroke in patients undergoing cardiac surgery (Selim, 2007). Stroke incidence has been reported to be 1.4% to 3.8% percent following coronary artery bypass grafting (CABG), 8.7% following aortic repair and 9.7% following double or triple valve surgery (Selim, 2007). Other surgery carries a lower risk of stroke, with the reported incidence of perioperative stroke following general surgery of 0.08% to 0.70%.

Another potential cause of swallowing disorder following surgery is intra-operative cranial nerve damage, such as injury to the recurrent laryngeal nerve during cardiac surgery (DiLisio, Mazzeffi, Bodian, & Fischer, 2013). In addition, ICU patients who have had surgery are likely to spend extended time in a supine position, increasing the risk of gastroesophageal reflux (Aderinto- Adike & Quigley, 2014), and will often have altered sensorium following surgery (Schenning & Deiner, 2015), two of the identified mechanisms for swallowing disorders in ICU (Macht et al., 2013).

1.3.2.3 Dysphagia following cardiothoracic surgery

In the survey of ICU admissions by Simpson and colleagues (2005), nearly one fifth (18.8%) of all patients were admitted for treatment following vascular surgery, with patients requiring valve replacements and bypass grafting in this group. This admission rate made vascular surgery the second most common reason for non-ED admissions. As with other ICU patients, the cardiothoracic population is at risk of developing post-operative dysphagia (Barker et al., 2009; Daly, Miles, Scott, & Gillham, 2016; Ferraris et al., 2001; Hogue et al., 1995). In a study by Hogue and colleagues (1995) investigating swallowing following cardiac surgery, all patients who demonstrated overt signs of dysphagia, including coughing while drinking, underwent videofluoroscopic swallow studies (VFSS). Ninety percent of the participants demonstrated aspiration, 22% of these without stimulating a cough response. By examining only those with an overt swallowing problem, it is likely that their method of participant selection would have missed a number of patients who were silently aspirating,

which suggests that the true prevalence of silent aspiration is greater than the figure reported by the authors.

In a recent study, Daly and colleagues (2016) audited the medical records of 190 patients who were intubated for more than 48 hours following cardiothoracic surgery. Details about each patient's diagnosis, surgery, recovery and swallowing ability were analysed. Forty-one (22%) of the patients were referred to Speech-language Therapy (SLT) during their recovery for assessment of suspected dysphagia and 33 (17%) were diagnosed as having some degree of dysphagia. Twenty-four of the patients with dysphagia underwent instrumental assessment of which 17 (70%) demonstrated silent aspiration. The authors concluded that implementation of a standardised protocol for referral to SLT would improve early identification of at-risk patients and potentially reduce the risk of aspiration and subsequent pneumonia. However, the authors failed to address patients who did not show overt signs of aspiration when eating and, as a result, were not identified by observational screening or clinical assessment. Although both studies offer valuable insight into the presence of post-extubation dysphagia in patients who have undergone cardiothoracic surgery, they do not sufficiently address the issue of silent aspiration in this population.

1.3.2.4 Post-extubation Dysphagia

Dysphagia may also occur as a complication of ventilation for respiratory failure. The occurrence of post-extubation dysphagia has long been reported in the literature as a complication of ICU treatment (Burgess, Cooper, Marino, Peuler, & Warriner, 1979). Reported prevalence of dysphagia after orotracheal extubation varies widely from 3% to as high as 58% (Ferraris et al., 2001; Hogue et al., 1995; Scheel et al., 2016), making it a significant contributor to dysphagia in the ICU population. The existing research into post-extubation dysphagia, including the prevalence and proposed causes, warrants in-depth evaluation.

1.3.3 *Summary*

When the swallowing process is disordered as a result of neurological impairment or injury, aspiration of food, fluid or saliva into the airways may occur. Aspiration may be overt or silent and, in the presence of additional risk factors, may lead to a number of serious consequences, including pneumonia. Dysphagia is associated with increased length of stay and cost of hospital treatment. Dysphagia occurs frequently in the ICU population due to neurological injury, ICU acquired weakness and surgery, cardiothoracic surgery, and orotracheal intubation. Post-extubation dysphagia is a frequent complication of orotracheal intubation and deserves further discussion.

1.4 *Post-extubation dysphagia*

A number of researchers have examined dysphagia in the post-extubation ICU population. Characteristics of 18 studies examining post-extubation dysphagia are outlined in Table 1. The variation in results can be partly attributed to the diverse patient populations studied and the diagnostic methods used. Many studies are retrospective in nature (Barker et al., 2009; Bordon et al., 2011; Daly et al., 2016; Macht et al., 2011; Malandraki, Markaki, Georgopoulos, Psychogios, & Nanasc, 2016; Padovani, Moraes, de Medeiros, de Almeida, & de Andrade, 2008; Rousou et al., 2000) or only include clinical assessment measures of dysphagia rather than instrumental assessment (Bordon et al., 2011; Brown et al., 2011; Kwok, Davis, Cagle, Sue, & Kaups, 2013; Macht et al., 2011; Padovani et al., 2008). Therefore, these studies are not considered to have robust methodology for detecting the true rate of dysphagia.

Table 1. Characteristics of Studies Examining Post-extubation Dysphagia.

Authors & Year	#	Population	Design	Selection	Intubation Criteria	Assessment Method (VFSS/VES)	Definition of Dysphagia	Dysphagia	Aspiration Total(Silent)	Resolution
Ajemian, Nirmul, Anderson, Zirlen & Kwasnik, 2001	48	General ICU	P	All	>48hrs*	VES	PAS \geq 6	56%	56%(25%)	63% on oral diet by discharge
Barker, Martino, Reichardt, Hickey & Ralph-Edwards, 2009	254	Post cardiac surgery	R	All	>48 hrs *	Clinical assessment +/- VFSS	Abnormal clinical assessment	51% **	NR	8% > 10 days to return to oral intake
Barquist, Brown, Cohn, Lundy & Jackowski, 2001	70	Trauma	P	All	>48 hrs	Control = Usual clinical assessment Experimental = VES	Control = PAS \geq 6 or clinical aspiration (suctioning of feeds from below vocal cords) Experimental = clinical aspiration	10%	Experimental Group = 14%(5%) Control Group = 1%(N/A)	No clinical aspiration > 96 hours post-extubation
Bordon, Bokhari, Sperry, Testa, Feinstein, et al., 2011	150	Trauma	R	All	>48 hrs	Clinical assessment	Abnormal clinical assessment	41% **	NR	NR
Brown, Hejl, Mandaville, Chaney, Stevenson, et al.,	291	Trauma	P	All	Any	Clinical assessment	Abnormal clinical assessment	51% **	NR	16% nil by mouth throughout hospital stay

2011										
Burgess, Cooper, Marino, Peuler & Warriner, 1979	64	Post cardiac surgery	P	All	Any	Evidence of radiopaque dye on chest x-ray (24 participants immediately post-extubation ¹ , 20 at 4hrs ² , 20 at 8hrs ³)	Evidence of radiopaque dye in trachea or below on chest x-ray	33% ¹ , 20% ² & 5% ³	33%(100%) ¹ , 20%(100%) ² & 5(100%)% ³	NR
Daly, Miles, Scott & Gillham, 2016	190 ^a	Post cardiac surgery	R	Suspected dysphagia	>48hrs	Clinical assessment +/- VFSS/VES	Abnormal clinical assessment, VES (23) or VFSS (1)	17%	NR(9%)	NR
De Larminat, Montravers, Dureuil & Desmonts, 1995	34	General ICU	P	All	>24hrs	Swallow latency, number and cough response to saline injected at epipharynx	Increased swallow latency, increased swallowing events, coughing with swallowing	NR ^b	NR	Swallowing latency significantly reduced by Day 7
El Solh, Okada, Bhat & Pietrantoni, 2003	84 ^c	Medical ICU	Pro	All	>48hrs*	VES	PAS \geq 6	44%	44%(13%) ^c	Dysphagia present in 30% at 5 days, 7% at 14 days and 7% at 6 weeks
Ferraris, Ferraris, Moritz & Welch, 2001	1042	Post cardiac surgery	P	All	Any	Screening, clinical assessment +/- VFSS	Abnormal screening ^d	3%	2%(NR)	4/16 patients with aspiration on VES required > 4 months,

										30/31 returned to normal diet by 6 months
Hafner, Neuhuber, Hirtenfelder, Schmedler & Eckel, 2008	295 ^e	General ICU	P	Suspected dysphagia ^e	Any [*]	VES	PAS \geq 6	56%	56%(17%) ^e	NR
Hogue, Lappas, Creswell, Ferguson, Sample, et al., 1995	844	Post cardiac surgery	P	Suspected dysphagia	Any ^f	VFSS	Abnormality in one element of swallowing on VFSS ^f	3% **	4%(<1%)	NR
Kwok, Davis, Cagle, Sue & Kaups, 2013	270	Trauma	P	Clinical assessment performed	>24hrs*	Clinical assessment	Abnormal clinical assessment	35% **	NR(37%) ^g	All resolved – no timeframe given
Leder, Cohn & Moller, 1998	20	Trauma	P	All	>48hrs	VES	PAS \geq 6	45%	45%(20%)	89% resumed oral diet by 10 days
Macht, Wimbish, Clark, Benson, Burnham, et al., 2011	2484	General ICU	R	Suspected dysphagia ^g	Any	Clinical assessment	Abnormal clinical assessment	15% ** ^h	NR(NR)	Dysphagia resolved during admission for 54%
Malandraki, Markaki, Georopoulos, Psychogios & Nanas, 2016	357	General ICU	R	All	Any	Clinical assessment +/- VFSS	Abnormal clinical assessment	23% ** ⁱ	NR(NR)	55% with mod/sev dysphagia NBM at discharge Presence of dysphagia associated with

										pneumonia & death
Noordally, Sohawon, De Gieter, Bellout & Verougstraete, 2001	21	General ICU	P	All	>48hrs	Clinical assessment, VES & +/- VFSS	Abnormal clinical assessment, VES or VFSS	NR	27% ^j (NR)	NR
Padovani, Moraes, de Medeiros, de Almeida & de Andrade, 2008	44	Brain injury	R	Suspected dysphagia	>48hrs*	Clinical assessment	Dysphagia Severity Scale and Functional Oral Intake Scale	57% ^k	NR(NR)	NR
Rosou, Tighe, Garb, Krasner, Engelman, et al., 2000	838	Post cardiac surgery	R	All	Any	VFSS	Abnormal VFSS ^l	3% ^{**}	NR(NR)	NR
Scheel, Pisegna, McNally, Noordzij & Langmore, 2016	59	General ICU	P	All	>48hrs	VES	PAS \geq 3	58%	22%(8%)	NR

#=number of participants, P=prospective, R=retrospective, VES=videoendoscopy of swallowing, VFSS=videofluoroscopy of swallowing, PAS=Penetration-Aspiration Scale, NR=not reported

* Excluded participants with tracheostomies

** Length of intubation a significant predictor

a Only files of patients referred for clinical assessment were reviewed (41 or 190 patients).

- b Did not have a cut-off for dysphagia, but swallow latency significantly increased in intubated participants. Nil difference in number of swallows or coughing.
- c 42 young (<65yrs) and 42 elderly (≥65yrs); 36% young and 56% elderly aspirated; 7% young and 20% elderly silently aspirated
- d A study nurse observed all participants and referred those with overt signs of dysphagia for clinical assessment, which included VFSS
- e Participants were referred for the study if they exhibited symptoms of dysphagia as displayed in Figure 3. Participant number includes all patients screened, but dysphagia prevalence is within only those participants referred for clinical exam.
- f Analysis performed separately for participants with and without tracheostomy. The elements of swallowing included time of oral transport, sensorimotor function, pharyngeal peristalsis, epiglottic closure and pulmonary aspiration
- g Authors did not specify how they identified silent aspiration
- h Only files of patients referred for clinical assessment were reviewed (446 of 2484 patients). There was a significant correlation between length of intubation and dysphagia when only participants without tracheotomy were included in analysis. Presence of tracheotomy was associated with dysphagia, but patients with tracheotomy were more likely to be referred for clinical assessment.
- i 5% of participants had mild dysphagia, 23% had moderate or severe according to clinical assessment
- j 27% aspirated on thin liquid, 18% on thickened water
- k Dysphagia prevalence is percentage of participants referred for clinical exam, not percentage of total admissions. 43% normal or functional, 7% mild dysphagia, 9% mild-moderate dysphagia, 11% moderate dysphagia, 11% moderate to severe dysphagia, 18% severe dysphagia
- l Dysphagia considered to be present when subjective signs and symptoms were confirmed with VFSS

The two studies reporting the lowest incidence of dysphagia post-extubation, both 3%, examined swallowing in patients after cardiac surgery (Ferraris et al., 2001; Hogue et al., 1995). In both studies, participants were assessed for dysphagia only if they demonstrated overt signs of aspiration, causing suspicion of oropharyngeal dysphagia. These participants underwent a videofluoroscopic swallowing study (VFSS). Aspiration was classified as the presence of barium contrast below the vocal cords. Hogue and colleagues, like many other researchers investigating post-extubation dysphagia, used the Penetration–Aspiration Scale (PAS) (Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996) to rate the presence, degree and response to penetration and aspiration. The authors considered dysphagia to be present if oral transport, sensorimotor function, pharyngeal peristalsis or epiglottic deflection were subjectively judged to be abnormal. Ferraris and colleagues (2001) considered dysphagia to be present in anyone who “experienced difficulty initiating a swallow or who had any symptomatic abnormality in swallowing physiology of the upper aerodigestive tract” (p. 1793) as observed by a research nurse at the screening stage. In both of these studies, the selection method would be unlikely to identify patients with sensory deficits who displayed no overt signs of dysphagia or aspiration. Also of note, Hogue and colleagues assessed only puree consistency on VFSS, which is less likely than thin fluids to be aspirated in individuals with neurogenic dysphagia (Clave et al., 2007). Collectively, these factors contribute to a reported prevalence of dysphagia that is likely below the true prevalence in the ICU population.

In four studies reporting much higher dysphagia incidence, ranging from 44% to 58% (Ajemian et al., 2001; El Solh et al., 2003; Leder et al., 1998; Scheel et al., 2016), every participant underwent videoendoscopy, regardless of the presence or absence of symptoms. Therefore, these studies may provide a more accurate estimate of the true prevalence of dysphagia in the ICU population. When comparing the studies, it is important to consider the

authors' definitions of dysphagia. Ajemian and colleagues, El Solh and colleagues and Leder and colleagues each defined dysphagia as a PAS score of six or greater, indicating the presence of material below the vocal folds, and reported a presence of aspiration in 56%, 44% and 45% respectively. Scheel and colleagues (2016) defined dysphagia as $PAS \geq 3$, which likely explains their higher reported rate of dysphagia at 58%. Scheel and colleagues (2016) reported an aspiration rate ($PAS \geq 6$) of 22%.

There are two other key differences that potentially contribute to the disparity in findings between the studies reporting lower incidence (Ferraris et al., 2001; Hogue et al., 1995) and the studies reporting a higher incidence of aspiration (Ajemian et al., 2001; El Solh et al., 2003; Leder et al., 1998; Scheel et al., 2016). First, the two studies with a lower reported incidence of dysphagia both used VFSS to diagnose aspiration while the studies with higher reported incidences all used videoendoscopic evaluation of swallowing (VES). There is evidence that clinicians rate penetration and aspiration viewed on VES as more severe compared to simultaneous VFSS (Kelly, Leslie, Beale, Payten, & Drinnan, 2006). As a result, participants in the VES groups may have been given higher PAS scores. Second, all participants in the studies with higher reported incidences were intubated for at least 48 hours. This is an important differentiation, as longer duration of intubation has been associated with increased risk of dysphagia in a number of studies (Barker et al., 2009; Brown et al., 2011; Hogue et al., 1995; Macht et al., 2011; Rousou et al., 2000).

It is worth noting that some studies enrolled participants with tracheotomies in situ (Bordon et al., 2011; Brown et al., 2011; Daly et al., 2016; Hogue et al., 1995; Leder et al., 1998; Macht et al., 2011), others excluded participants with tracheotomies (Ajemian et al., 2001; Barker et al., 2009; El Solh et al., 2003; Hafner et al., 2008; Noordally et al., 2011; Padovani et al., 2008; Scheel et al., 2009) and some did not specify whether their participants included patients with tracheotomies (Barquist et al., 2001; de Larminat et al., 1995; Ferraris

et al., 2001; Rousou et al., 2000). Ajemian and colleagues (2001) and El Solh and colleagues (2003) cited the reported link between tracheotomy and dysphagia as the reason for excluding these participants. Indeed, several of the studies that included participants with tracheotomies reported an association between the presence of a tracheotomy and dysphagia (Brown et al., 2011; Daly et al., 2016; Hogue et al., 1995; Macht et al., 2011). However, three of these studies also reported that length of intubation was a significant predictor of dysphagia (Brown et al., 2011; Daly et al., 2016; Macht et al., 2011). Given that prolonged intubation is an indication for tracheotomy (Cosgrove & Carrie, 2015), it is possible that the increased risk of dysphagia in this cohort is due to prolonged intubation, rather than tracheotomy. Recent research does not support an independent link between tracheotomy and dysphagia (Donzelli, Brady, Wesling, & Theisen, 2005; Jin, Kyoung, Gi, Min, & Ju, 2012; Leder & Ross, 2010). To avoid this potential complication, it may be best to exclude participants with tracheostomies from future research studies focusing on dysphagia post-extubation or, at a minimum, to analyse this cohort separately.

1.4.1 Silent aspiration post-extubation

Silent aspiration occurs in the post-extubation population, but it is difficult to determine how common this is due to a wide range of methods reported in the literature. Studies examining post-extubation silent aspiration in a general ICU population report prevalence of 8% (Scheel et al., 2016), 17% (Hafner et al., 2008) and 25% (Ajemian et al., 2001). Hafner and colleagues (2008) reported silent aspiration prevalence only as measured in participants who presented with overt signs of aspiration. Individuals who aspirate silently are less likely to be identified through observation of overt swallowing difficulties and were therefore less likely to be enrolled as participants. Because of this study design, their reported prevalence of 17% may not be representative of the true prevalence in the ICU population.

Scheel and colleagues (2016) and Ajemian and colleagues (2001) employed similar methods to each other with all participants undergoing VES within 48 hours of extubation. The reason for the large discrepancies between the results of the two studies is unclear, but may be related to the age of participants. El Solh and colleagues (2003) reported a higher frequency of silent aspiration in participants older than 65 years of age (20%) than in participants younger than 65 years of age (7%). Ajemian and colleagues (2001) report the mean age of their participants classified into “aspirators” and “non-aspirators”, 69 years and 66 years respectively. Scheel and colleagues (2016) reported a slightly lower mean age of their total participant cohort at 58 years. Other explanations may include a difference in median lengths of intubation across participants, which was not consistently reported, or differences in the patient population.

There is very limited data in the literature regarding post-extubation silent aspiration in patients who have been intubated for less than 48 hours. Few prospective studies have employed instrumental assessment and all but two that did included only participants who had been intubated for greater than 48 hours (Ajemian et al., 2001; Barquist et al., 2001; El Solh et al., 2003; Kwok et al., 2013; Leder et al., 1998; Scheel et al., 2016). The two studies that included a range of intubation times only included participants who had been referred for a swallowing assessment due to suspected dysphagia (Hafner et al., 2008; Hogue et al., 1995), which, as mentioned previously, is likely to result in lower reported rates of silent aspiration.

1.4.2 Impact of length of intubation on swallowing

The length of orotracheal intubation is frequently reported in the literature as a significant predictor of dysphagia (Barker et al., 2009; Bordon et al., 2011; Brown et al., 2011; Hogue et al., 1995; Kwok et al., 2013; Macht et al., 2011; Malandraki et al., 2016; Rousou et al., 2000). In a study by Bordon and colleagues (2011), the number of ventilator

days was the only significant, independent predictor of post-extubation dysphagia in 151 trauma patients who required orotracheal intubation greater than 48 hours. The risk of post-extubation dysphagia increased in these subjects by 14% for each day on the ventilator. This finding was supported by a retrospective review of ICU patients who had undergone a bedside swallowing evaluation (Macht et al., 2011). Intubation for greater than seven days was an independent predictor of severity of dysphagia, even when patients with acute neuromuscular disease or CVA were excluded.

Wide-ranging methodologies between studies again make it difficult to compare results. Several studies investigating the impact of the length of intubation on post-extubation dysphagia only included participants if they had been intubated for 48 hours or more (Ajemian et al., 2001; Barker et al., 2009; Barquist et al., 2001; Bordon et al., 2011; Daly et al., 2016; El Solh et al., 2003; Leder et al., 1998; Noordally et al., 2011; Padovani et al., 2008; Scheel et al., 2016). Several studies focused only on specific populations and the results cannot necessarily be extrapolated to the general ICU population (Brown et al., 2011; Burgess et al., 1979; Ferraris et al., 2001; Hogue et al., 1995; Rousou et al., 2000). Some studies did not employ instrumental assessment and may not be reliably identifying participants with dysphagia (Brown et al., 2011; Burgess et al., 1979; Ferraris et al., 2001; Macht et al., 2011; Malandraki et al., 2016). In their 2010 systematic review of literature on the incidence of dysphagia in this population, Skoretz and colleagues commented that the effect of duration of orotracheal intubation on dysphagia could not be determined because the studies they reviewed were heterogeneous and there was insufficient evidence to draw strong conclusions (Skoretz, Flowers, & Martino, 2010). There is a gap in the literature regarding the relationship between length of intubation and presence of dysphagia, particularly short-term intubation.

1.4.3 Resolution of post-extubation dysphagia

While post-extubation dysphagia is relatively common, it usually resolves. In the majority of cases reported in the literature, dysphagia resolved by discharge from hospital (Ajemian et al., 2001; Barker et al., 2009; Brown et al., 2011; de Larminat et al., 1995; El Solh et al., 2003; Ferraris et al., 2001; Leder et al., 1998; Macht et al., 2011; Rousou et al., 2000). Most research groups who considered resolution of dysphagia measured it as return to oral diet (Ajemian et al., 2001; Barker et al., 2009; Brown et al., 2011; Ferraris et al., 2001; Kwok et al., 2013; Leder et al., 1998), which doesn't capture subtle changes or definitively rule out on-going aspiration. El Solh and colleagues (2003) repeated VES on patients with dysphagia on days 5 and 14 and at 6 weeks. With an initial prevalence of aspiration ($PAS \geq 6$) of 44%, this reduced to 30% and 7% at each respective follow-up. None of the studies have looked at changes in swallowing in the hours immediately following extubation, despite the clinical relevance of this question. Clinicians routinely decide when to initiate oral intake after extubation or if alternative nutrition is needed. Future studies should consider reviewing swallowing within the initial hours post extubation to determine how rapidly post-extubation can resolve.

1.4.4 Causes of Post-extubation Dysphagia

The exact aetiology of dysphagia after oral intubation is unknown, but proposed possibilities include laryngotracheal injury (Brown et al., 2011; Colice, 1992; de Larminat et al., 1995; El Solh et al., 2003; Tolep, Getch, & Criner, 1996), neurological adaptation (Tanaka, Isono, Ishikawa, & Nishino, 2005), weakness from muscle atrophy (Brown et al., 2011; DeVita & Spierer-Rundback, 1990; Tolep et al., 1996), the use of neuromuscular blocking agents (Brown et al., 2011; de Larminat et al., 1995; Tolep et al., 1996), disruption in respiration (de Camargo, Ono, Park, Caruso & Carvalho, 2010) or underlying neurological illness (Tolep et al., 1996). After extubation, any individual patient is likely to have multiple aetiologies impacting swallowing. When considered in the context of Macht and colleagues'

(2013) mechanisms for the development of swallowing disorders in ICU, these potential aetiologies may cause dysphagia through injury to the larynx, reduction in laryngeal sensation, neuromuscular weakness, or dyssynchronous breathing.

Rapid and complete movement of the laryngeal structures is essential for safe and efficient swallowing and laryngeal trauma from intubation can contribute to dysphagia in the ICU population through two proposed mechanisms: injury to the laryngeal tissues causing oedema, ulceration and granulation of the tissue or damage to the recurrent laryngeal nerve (RLN) as a result cuff pressure (Colton House et al., 2011). Examples of laryngotracheal injury are well documented in the literature and include subglottic, arytenoid and vocal cord oedema, as well as granulation and ulceration of the vocal cords (Colton House, Noordzij, Murgia, & Langmore, 2011; Scheel et al., 2016; Tadie et al., 2010). Colton House and colleagues (2011) performed VES within 24 hours of extubation on 61 adult ICU patients who were intubated for more than 48 hours and reported that 100% of participants had some degree of laryngeal injury. Colice and colleagues (1989) reported that 52% of ICU patients had moderate to severe laryngeal damage following four days of intubation. Two of the subjects in the study by Colice and colleagues (1989) had such severe ulceration of their vocal cords that they couldn't achieve laryngeal closure and aspiration of fluids was observed on laryngoscopy. Both subsequently developed recurrent aspiration pneumonia. Similarly, Scheel and colleagues (2016) reported a significant correlation between PAS scores and findings of vocal process granuloma and left or right vocal cord oedema.

The correlation between duration of intubation and severity of laryngeal injury is disputed (Bishop, Hibbard, Fink, Vogel, & Weymuller, 1985; Colice, 1992; Colton House et al., 2011; Kastanos, Miro, Perez, Mir, & Agusti-Vidal, 1983; Peppard & Dickens, 1983; Postma et al., 2007; Stauffer, Olson, & Petty, 1981; Tadie et al., 2010; Tanaka et al., 2005; Vila et al., 1997; Whited, 1984). Bishop commented on the challenges associated with

determining the significance of prolonged intubation in his 1989 discussion paper on the causes of laryngotracheal injury following orotracheal intubation.

“In human studies, the data are always confounded by the fact that the patients intubated the longest are almost always the sickest patients, with the largest numbers of infections, the most episodes of hypertension, etc.” (p. 185)

In a commentary on the systematic review by Skoretz and colleagues (2010), Heffner (2010) proposes that laryngeal injury can occur with relatively short periods of intubation. This is supported by a study by Bishop and colleagues (1985) in which 14 dogs were intubated and underwent laryngeal and tracheal endoscopy at days one, seven, 14 and then every two weeks until death to observe for laryngeal damage. Dogs were killed at day one, two weeks, four weeks, six weeks and 12 weeks and their larynges were removed and examined. There was a significant increase in ulceration of the laryngeal mucosa between day one and day seven, but no significant increase beyond that point. Stauffer and colleagues (1981) observed airway lesions on post-mortem examination after as few as seven hours of intubation, supporting the argument that laryngeal injury can occur after short periods of orotracheal intubation.

There is limited data on the resolution of intubation injury in the general ICU population (Colice, 1992; Kastanos et al., 1983; Peppard & Dickens, 1983; Stauffer et al., 1981; Whited, 1984). The data that exists suggests that laryngeal injuries do improve, but not always rapidly. Colice and colleagues (1992) performed laryngoscopy within 24 hours of extubation and then performed follow-up laryngoscopies every two weeks until either assessment was normal or a moderate or severe adverse effect was recognized. They reported that median time to resolution of laryngeal injury was four weeks and 92% of the subjects had a normal exam by eight weeks. Kastanos and colleagues (1983) completed an initial laryngoscopy within two weeks of extubation then repeat laryngoscopies every two months.

By three months, 84% had a normal laryngoscopy. Combined, these studies suggest that the vast majority of laryngeal intubation injuries resolve within two to three months. Both of these studies report similar recovery times despite different enrolment criteria: Kastanos and colleagues (1983) enrolled patients with a minimum of 24 hours of intubation while Colice and colleagues (1992) employed a minimum of four days of intubation. Intubation injuries may be as likely to occur and as long lasting following short-term intubation compared to longer-term intubation. This may offer a possible explanation for the existence of dysphagia after short-term intubation. It is tempting to compare recovery times for post-extubation dysphagia and laryngeal injury from intubation, but lack of standardisation and reporting of timeframes for follow-up make this impossible.

Although much of the data presented is from studies that are 20 to 30 years old, laryngeal injury continues to occur with modern equipment and techniques. One very recent study by Nordang, Lindholm, Larsson and Linder (2016) compared the traditional endotracheal tube to a new tube that the authors hypothesized would cause fewer laryngeal injuries. Median length of intubation was 21 hours in the experimental group and 22 hours in the control group. Laryngoscopy performed within 24 hours of extubation revealed laryngeal abnormalities in all participants. At the follow-up laryngoscopy, performed between three and six weeks post-extubation, 11 participants from each group had persistent laryngeal pathology that was classified as more than erythema. There was not a significant difference between the experimental and control groups. These recent data suggest that, despite evolving equipment and methods, laryngeal injury continues to occur as a result of intubation and can persist for weeks.

In some cases, contact of the endotracheal tube cuff with the tracheal mucosa can cause erosion and damage to the recurrent laryngeal nerve (RLN), which enters the larynx between the thyroid and cricoid cartilages (Colton House et al., 2011). Damage is

exacerbated by high cuff pressures. Colton House and colleagues observed vocal cord immobility in 39% of ICU patients who were intubated for 48 hours or more and proposed injury to the RLN as the cause. These findings have been supported by other studies, which also attributed the impairment in mobility to high cuff pressures (Tadie et al., 2010). In a study by Hamdan, Sibai, Rameh and Kanazeh (2007), cuff parameters, specifically pressure and volume, were the most important variables associated with intubation related dysphagia. Collectively, these studies provide evidence that pressure from the endotracheal cuff has a detrimental effect on the RLN, which provides efferent innervation to the vocal cords, critical for airway protection. This can occur following even short periods of intubation and the resulting impairment of laryngeal closure places patients at high risk of aspiration.

Although contact between the endotracheal tube components and the mucosa of the larynx and trachea can cause impairment of laryngeal function, a study by Tanaka and colleagues (2005) suggests that there are additional causes of laryngeal impairment. They compared two types of artificial airways: a low pressure cuffed endotracheal tube (ETT), which passes through the glottis and terminates in the trachea, and the laryngeal mask airway (LMA), which terminates just superior to the laryngeal vestibule. The authors hypothesized that use of a LMA would preserve laryngeal reflexes post-extubation. Twenty patients undergoing general anaesthesia and intubation for minor elective surgery were randomly assigned to receive either ETT or LMA. Laryngeal responses and the angle of the vocal cords were assessed under non-opioid anaesthesia before placement of the tube. After the surgery was completed, the effect of the muscle relaxant was fully reversed and the testing was repeated. Although glottal angle was only affected in the ETT group, cough reflex in response to water injected into the glottis was absent in all participants across both groups. This is the only study that has specifically examined the effect of intubation on the cough reflex and is important to highlight. The high prevalence of silent aspiration in the ICU

population may be related to this impairment of cough reflex. Tanaka and colleagues (2005) proposed that either the presence of the tube in the pharynx or larynx or noxious anaesthetics present in the airway could evoke accommodation or adaptation of the receptors and/or neural pathways, thus blunting the airway reflexes.

There is less evidence regarding other proposed causes of dysphagia, including muscle atrophy, lingering neuromuscular blocking agents, underlying neurological illness, and the disruption of breathing and swallowing patterns, specific to the post-extubation population. Muscle atrophy can occur after relatively short periods of inactivity. Atrophy of the diaphragm can occur after just a few days of mechanical ventilation (Levine et al., 2008). This could cause aspiration, but would not explain the frequent occurrence of silent aspiration in this population (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). The disruption of the typical expiration-swallow-expiration cycle that de Camargo and colleagues (2010) observed in a single patient who had been intubated for four days, if indeed it did occur routinely after extubation, would also not explain silent aspiration. Regarding residual neuromuscular blocking agents (de Larminat et al., 1995; Tanaka et al., 2005) and underlying neurological illness (de Larminat et al., 1995; El Solh et al., 2003; Macht et al., 2011), studies that controlled for these factors continued to show that dysphagia was common, indicating that they were not the sole aetiology. Lingering residual neuromuscular blocking agents and analgesics would also not account for the documented cases of dysphagia that are slow to resolve, persisting long after these agents are out of the patient's system. It is most likely that any individual patient who experiences dysphagia after extubation would be impacted by a combination of the factors above, affecting one individual to a greater or lesser extent than another. This conundrum makes it very difficult for studies to determine the cause of dysphagia; any attempts would require a very large sample size, which has not been done in this field of research.

1.4.5 *Summary*

Oropharyngeal dysphagia is a well-documented complication of orotracheal intubation in the ICU population. The reported prevalence varies widely between studies due to varied study methodology. In particular, the enrolment of only those patients who display overt signs of dysphagia automatically excludes many silent aspirators. Length of intubation has been reported to correlate with the presence of dysphagia, but very few studies have examined the impact of short (<24 hours) periods of intubation. The aetiology of post-extubation dysphagia is not fully understood, but laryngotracheal injury resulting from orotracheal intubation is well documented and often cited as a cause of dysphagia. In reality, the ICU patient group is extremely complex and dysphagia in any individual is likely a result of a number of factors.

1.5 *Assessment of Swallowing in ICU*

Despite the high prevalence of dysphagia in ICU patients after extubation, swallowing screening and clinical assessment does not routinely occur in this population. In a survey of American SLTs who provide swallowing assessment to patients who have been mechanically ventilated, only 3% reported that they assess all recently extubated patients (Macht et al., 2012). There is little guidance in the literature regarding the role of the SLT in assessing dysphagia after extubation. Baumgartner, Bewyer and Bruner (2008) provide an overview of the role of SLT in the ICU. The authors suggest that patients who have had prolonged endotracheal intubation should be referred to SLT for clinical assessment prior to initiating oral intake, citing the studies by Ajemian and colleagues (2001), Colice, Stukel and Dain (1989) and El Solh and colleagues (2003), who all reported impairment in participants after a minimum of 48 hours of intubation. In a paper discussing the evaluation of dysphagia after orotracheal intubation and tracheostomy, Goldsmith (2000) states that there is not a single recommended method for assessing or managing patient who have recently been extubated.

However, assessment should include a careful consideration of all contributing factors and, the author states, should be diagnostic rather than screening because of the inability of existing screening tools to detect silent aspiration. A screening tool that is able to detect silent aspirations, or the risk of silent aspiration, would be beneficial in this population. Goldsmith also advises that patients remain nil-by-mouth for 24 hours following orotracheal extubation to allow healing of laryngeal injury and return of laryngeal sensation (Goldsmith, 2000). However, with limited data on the recovery of swallowing in the first 24 to 48 hours following extubation, there is little support in the literature for this approach.

Scheel and colleagues (2016) compared the results of swallowing assessments of participants who were assessed within 24 hours of extubation to results of patients who had been intubated for less than 24 hours and found no significant differences. The authors suggested that delaying oral intake for 24 hours may not change the outcome of the swallowing assessment and more rapid assessment may offer the benefits of engaging the swallowing mechanism sooner and avoiding placement of nasogastric tubes. Despite the clear need for swallowing assessment in at least some patients after extubation, none of the international professional organisations that oversee SLT services, including the New Zealand Speech-Language Hearing Association, American Speech, Language and Hearing Association, or Royal College of Speech-Language Therapists, have clear guidelines specifically for the screening, assessment or management of recently extubated patients.

1.5.1 Screening for a swallowing disorder

Screening for a disease is a way to identify individuals who likely have that disease within a given population. Screening for dysphagia is well established in the literature, particularly in individuals with neurogenic disorders. In a prospective audit of 2,352 stroke admissions, odds of developing pneumonia were three times greater for patients who did not undergo a formal dysphagia screening (Hinchey et al., 2005). A number of screening tools for

dysphagia exist, although, in many cases, the strength of evidence is variable (Daniels, Anderson, & Willson, 2012). A screening tool should ideally be easy to administer and inexpensive, have high sensitivity and specificity, and shouldn't require specialist knowledge to complete (Kertscher, Speyer, Palmieri, & Plant, 2014). Given the reported incidence of dysphagia and aspiration after orotracheal intubation in the ICU population and the relationship between aspiration and poor patient outcomes, it would seem beneficial to screen all patients after extubation to identify those at risk for aspiration. A screening should ideally include a mechanism for identifying which patients are at increased risk of silent aspiration.

1.5.2 Clinical swallowing assessment

The clinical swallowing assessment is typically the first step towards identifying dysphagia and determining a management plan. A clinical assessment typically consists of a review of a patient's medical history, observations of the patient's communication and cognitive abilities, examination of the structure of the oral cavity, including the condition of the teeth and mucosa, tests of oromotor and sensory function, and trials of food and fluid (Carnaby-Mann & Lenius, 2008). Factors identified in any phase of the assessment may indicate an increased risk of dysphagia. The clinician synthesizes these observations and creates a hypothesis regarding the presence or absence, cause and nature of dysphagia and begins to formulate a management plan (Carnaby-Mann & Lenius, 2008).

Although clinical assessment provides vital information, its limitations need to be carefully considered. In a study by McCullough and colleagues (2001), specificity of the clinical assessment was reported to be 82% while sensitivity was just 68%. These figures indicate that the clinical assessment may do a reasonable job of ruling out dysphagia, but underestimates its presence. The authors also reported that most components of the clinical assessment were not valid on their own. Clinical assessment is particularly poor at identifying individuals who aspirate silently as silent aspiration cannot be detected on clinical assessment

due to the absence of outward signs such as coughing (Ramsey, Smithard, & Kalra, 2003). Because silent aspiration is common in the ICU post-extubation population, standard clinical assessment as outlined above is not sufficient for this population and instrumental assessment should be considered.

1.5.3 *Instrumental assessment*

Use of instrumental assessment enables the clinician to further diagnose the presence of dysphagia, define pathophysiology and plan treatment, including use of compensatory strategies and rehabilitative techniques. Because the majority of the swallowing process cannot be externally observed, instrumentation that allows a clinician to visualise internal structure and function in a dynamic way offers clear advantages. There are two primary methods of instrumental assessment: videofluoroscopy and videoendoscopy.

1.5.3.1 Videofluoroscopic Swallowing Study (VFSS)

VFSS is generally considered the “gold standard” of swallowing assessments (O’Donoghue & Bagnall, 1999). VFSS allows visualisation of bolus flow, through sequential radiographic images, from the mouth, through the pharynx and into the oesophagus. It also allows the assessor to visualise the movement of deep structures, such as the hyoid, which are not visible with non-radiographic imaging. Aspiration can be identified and the timing, subjective judgement of amount and subsequent response can be documented. In addition, VFSS provides an opportunity to trial compensatory strategies, such as texture modification or positioning, and to judge the impact on swallowing. Information gained about the physiology of swallowing is then used to guide rehabilitation (Martin-Harris & Jones, 2008).

There are limitations of VFSS, including the use of expensive equipment and exposure of individuals to radiation (Schröter-Morasch, Bartolome, Troppmann, & Ziegler, 1999). In addition, some patients are not able to participate in VFSS due to transferring or positioning restrictions, as with the critically unwell or obese patient, or because the VFSS

cannot be performed in a timely manner (Langmore, Schatz, & Olsen, 1988). The ICU post-extubation population often have very restricted mobility and instrumental assessment that could be used at bedside may be more suitable. For this reason, VES may be the preferred method of instrumental assessment for this population.

1.5.3.2 Videoendoscopy of Swallowing (VES)

Langmore, Schatz and Olsen first described the fiberoptic endoscopic evaluation of swallowing (FEES) protocol in 1988. Nasoendoscopy had long been employed as a means of evaluating the structure and function of the larynx, but Langmore and colleagues were first to document a protocol for performing dynamic swallowing assessment during nasendoscopy. The protocol they established has changed little over the more than 25 years since that publication. However, contemporary deviations to their original protocol are often referred to as VES. The endoscope is passed through the inferior nasal meatus until the velopharyngeal port is in view. The individual is asked to dry swallow to assess function of the velopharyngeal port. The scope is then progressed forward and down until the tip of the scope is positioned in the oropharynx. The presence, amount, consistency and location of secretions are noted and competence of the vocal cords assessed. The patient consumes boluses of food and liquid, usually liquid boluses of 5ml and 10ml and a puree bolus of 10ml as a minimum. Any type of food can be given during the study, depending on the status of the individual and goal of the assessment. All boluses are dyed blue or green so they can be easily visualised against the structures of the larynx and pharynx, which range in colour from white to pink to red.

The pharynx and larynx can be observed before and after swallowing, but during swallowing there is “white out” of the image when the pharyngeal muscles contract and obscure the camera view (Langmore et al., 1988). Premature spillage and pre-swallow penetration and aspiration can be observed prior to initiation of swallowing. After

swallowing, the assessor can observe the presence of residue, laryngeal penetration and aspiration and attempts to clear these by dry swallowing, throat clearing or coughing. The tip of the scope can be used to gently probe the pharyngeal and laryngeal structures as a gross assessment of sensitivity. If an individual does not respond to this probing, the assessor may assume that the individual would not respond to aspirate.

VES offers some key benefits over VFSS. VES is easily portable and can be performed at the patient's bedside, making it possible to assess very unwell, bedbound or obese patients. VES also allows the assessor to view secretions and make judgements about a patient's ability to manage secretions. The presence of pooled secretions has been shown to correlate with the presence of laryngeal penetration, aspiration and diet recommendations (Donzelli, Wesling, Brady, & Craney, 2003; Murray, Langmore, Ginsberg, & Dostie, 1996). VES allows for visualisation of the surface of the pharynx and larynx and identification of laryngeal pathology, which has also been linked to the presence of aspiration on videoendoscopy in recently extubated ICU patients (Scheel et al., 2016). When the results of simultaneous VFSS and VES are compared, with VFSS as the gold standard, the validity of VES to detect laryngeal penetration and aspiration is excellent (Aviv, 2000; Rao, Brady, Chaudhuri, & Wesling, 2003; Schatz, Langmore, & Olsen, 1991). There is some evidence that clinicians rate penetration and aspiration viewed on VES as more severe compared to VFSS. In a study by Kelly and colleagues (2006), participants underwent a simultaneous VES and VFSS. SLTs rating the studies consistently assigned a higher PAS score to the VES study, indicating that they detected laryngeal penetration and aspiration more often during VES than VFSS. This tendency needs to be kept in mind when interpreting VES. VFSS and VES have demonstrated similar inter-rater reliability for PAS ratings (Kelly et al., 2006).

1.5.3.2.1 Patient Tolerance of VES

Contraindications for VES include acute facial fracture, recurrent or persistent epistaxis, obstruction of both nares, severe agitation and inability to participate in the procedure (Leder & Murray, 2008). However, VES is generally well tolerated by patients. In a cohort of 300 acute stroke patients who underwent VES within the first few days of stroke onset, 6% of participants had a self-limiting nosebleed (Warnecke, 2009). There were also statistically significant changes in systolic blood pressure, heart rate and oxygen saturations. However, the authors considered all effects to be mild and no participant suffered a serious adverse effect. In the same study, 30% of participants rated the procedure, when done without topical anaesthesia, as “not uncomfortable”, 53% found it “mildly uncomfortable”, 13% found it “moderately uncomfortable, and only 3% found it “severely uncomfortable” (Warnecke, 2009). This study was conducted in acute stroke patients and the tolerance may differ in ICU patients, but has not been tested. ICU patients may be more likely to be influenced by anaesthetics and sedation or may be better able to follow instructions and may tolerate the procedure better. Conversely, some ICU patients may be agitated and find VES less comfortable. Further research on patient tolerance of VES in the ICU population would be beneficial.

When Langmore and colleagues first described FEES in 1988, the authors advised against the application of topical anaesthetic to the nares. This was based on evidence that the urge and ability to swallow was impaired after patients gargled a 2% lidocaine solution (Sider, Mintzer, Deschler, Kim, & Weinberg, 1983). In a study by Bastian and Riggs (1999) to determine the importance of intact sensation in swallowing, 13 participants underwent VES before and after application of lidocaine to the oral cavity, oropharynx, hypopharynx, larynx and subglottis. Ten participants in that study demonstrated a change in swallowing physiology. Although the authors concluded that normal swallowing could occur with

anaesthesia of the upper aerodigestive tract, it is clear from the results that liberal application of anaesthetic has the potential to alter swallowing.

In both of these studies however, the researchers were attempting to completely block sensation in the pharynx; the former to reduce involuntary swallows during radiographic procedures and the latter to determine the role of sensation in swallowing. The liberal use of topical anaesthetic in these studies is quite different to judicious and focused use during VES and the results are of limited application in the VES context. Indeed, during VES a small amount of anaesthetic is applied to the nares only. Johnson, Belafsky and Postma (2003) investigated the effect of bilateral nasal application of 4% cocaine solution on laryngeal sensation. The dose they selected reflected typical use for nasendoscopy. There was no significant difference in laryngeal responsiveness before or after topical anaesthetic and the authors reported that a small amount of anaesthetic to the nares does not appear to affect laryngeal sensation (Johnson et al., 2003).

Researchers from Wake Forest Baptist Medical Centre and Boston University Medical Centre collaborated in a series of three research studies to specifically investigate the effect of different doses of anaesthetic on swallowing during VES, both in healthy individuals and individuals with dysphagia. In the first study by Lester and colleagues (2013), healthy individuals underwent two VESs, 10 days apart. Participants were randomised to receive either the anaesthetised condition, with 1ml of lidocaine, or non-anaesthetised condition first, followed by the alternate condition. Each VES was reviewed by an SLT blinded to the condition under which it was performed. The authors reported a 1ml dose of 4% lidocaine did result in a statistically significant increase in penetration and aspiration events in the anaesthetised condition ($PAS \geq 1$ in 11% vs 3%). However, the clinical significance of this is negligible as the average PAS score with anaesthetic was only 0.16 higher (1.05 vs. 1.21), indicating a very mild impairment of swallowing. In the second study

by Fife and colleagues (2014), participants with dysphagia underwent two VESs, the first without anaesthesia and the second with 0.5ml of lidocaine, within a single clinic visit. VES recordings were again reviewed by SLTs blinded to the use of anaesthesia. The authors reported a non-significant trend towards increased PAS scores in the anaesthetised condition. And finally, O'Dea and colleagues (2015) completed a similar study examining the effect of 0.2ml lidocaine on swallowing during VES. Participants again underwent a VES without anaesthesia, but with decongestant, immediately followed by a VES with anaesthesia. The authors reported no significant difference in PAS score or residue between conditions. A limitation of these studies is the use of PAS score. It is commonly used in dysphagia literature, but it is not an interval scale. When reporting change in PAS scores it is important to consider that a change from 2, penetration that is cleared to 3, penetration that is not cleared is arguably less significant than a change from a 7, aspiration that triggers an attempt to clear, to 8, aspiration that does not trigger a response. Comparing mean PAS scores or changes in PAS scores can be problematic.

Lamvik (2016) investigated the impact of topical nasal anaesthesia on pharyngeal pressure by performing pharyngeal manometry on participants who were randomised to an experimental group receiving nasal anaesthesia and lubricant and a control group receiving only lubricant. Both the participant and researcher were blinded to the condition. Lamvik reported a lower mean pharyngeal during dry swallowing with anaesthesia when compared to the placebo group ($p=.020$), but a higher maximum pressure in the same condition. These differences did not translate to liquid swallows (Lamvik, 2016). Although in a clinical setting this difference may be unimportant, in a research setting even small changes in swallowing may influence sensitive measures, resulting in false conclusions.

There is mixed evidence regarding the impact of anaesthesia on patient comfort. All three of studies by the Wake Forest and Boston University Group reported significantly less

pain and improved tolerance for the participants with anaesthesia. It is important to note that the participants in the studies by Lester and colleagues (2013) and Fife and colleagues (2014) were not blinded to the use of anaesthesia. This may have biased their response questions regarding subjective ratings of pain. Leder, Ross, Briskin and Sasaki (1997) compared patient comfort during nasendoscopy with a topical anaesthetic, a vasoconstrictor and placebo in a randomised and double-blinded study. The authors reported there was no difference in patient comfort between the three groups with the majority of participants reporting no or mild discomfort. Their results are supported by those of Lamvik (2016), who reported no significant difference in procedure tolerance between participants receiving nasal anaesthesia prior to manometry and participants receiving a placebo. Considered alongside evidence that larger doses of topical anaesthetic can alter swallowing (>.5ml lidocaine), but small doses have no impact, it is advised that small doses of lidocaine may be safely used, but may not effect patient comfort and are not necessary for completion of VES.

1.5.3.2.2 Penetration-Aspiration Scale

The Penetration-Aspiration Scale (PAS) (Figure 6) was designed by Rosenbek and colleagues as a tool for researchers and clinicians to describe penetration and aspiration events observed on VFSS (Rosenbek et al., 1996). It is an 8-point ordinal scale, which classifies the depth of penetration or aspiration, the response to penetrated and aspirated material and the effectiveness of that response. The PAS was originally designed for VFSS interpretation, although reliability has also been established with VES (Colodny, 2002). A score of two through 5 is classified as airway penetration and a score of 6 or greater is classified as aspiration.

1. Material does not enter the airway.
2. Material does not enter the airway, remains above the vocal folds, and is ejected from the airway.
3. Material does not enter the airway, remains above the vocal folds, and is not ejected from the airway.
4. Material enters the airway, contacts the vocal folds, and is ejected from the airway.
5. Material does not enter the airway, remains above the vocal folds and is ejected from the airway
6. Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway
7. Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort
8. Material enters the airway, passes below the vocal fold, and no effort is made to eject

Figure 6. The 8-point Penetration - Aspiration Scale.

From “A penetration – aspiration scale”, by J. C. Rosenbek, J.A. Robbins, E. B. Roecker, J. L. Coyle, & J. L. Wood, 1996, *Dysphagia*, 11(2), p. 93-98. Copyright 1996 by Springer. Reprinted with permission.

The PAS is often used by researchers, but does have limitations. It is purported to be an ordinal scale, with a score of one indicating a normal swallow and a score of eight assigned to the most severely impaired swallow, with material passing below the vocal cords

without stimulating a cough. When material enters the airway, contacts the vocal cords and is not ejected, this is a score of 5. This situation is arguably more severe than when material passes below the cords and is ejected out the airway by a strong and prompt cough, which is scored as 6. It is not an interval scale and the degree of severity between each step is not equal.

1.5.4 Summary

The multidisciplinary team employs a range of screening and assessment tools to identify and diagnose dysphagia in the ICU patient depending on local protocol and practice. Given the high prevalence of silent aspiration in this population, screening and assessments would ideally be designed to identify those patients who are at risk of silent aspiration. Because of the limitations of clinical assessment, instrumental assessment is essential to accurately diagnose dysphagia. In the ICU setting, VES offers several benefits, including portability and the ability to view secretions and laryngeal pathology. VES is well tolerated and is the preferred instrumental assessment tool for the critically ill patient.

1.6 Cough Reflex Testing

Given the prevalence of silent aspiration in the ICU post-extubation population, the ability to assess airway protection offers clear advantages. The cough reflex is one of the key airway protection reflexes. Assessment of the cough reflex after extubation may offer useful insight into an individual's risk of silent aspiration and a close look at CRT research is warranted.

1.6.1 History of Cough Reflex Testing

Testing of the cough reflex was developed in the 1950s to aid development of cough medicines (Bickerman & Barach, 1954; Bickerman, German, Cohen, & Itkin, 1957). Participants were given various experimental cough medicines and then given tussigens,

substances known to stimulate cough. The effectiveness of the trial medicine was determined by its ability to attenuate the cough response. In the last 20 years, CRT has been further developed to test integrity of cough in patients with disease with the goal of developing a screening tool to identify individuals with dysphagia (Addington, Stephens, Gilliland, & Rodriguez, 1999; Addington, Stephens, Ockey, Kann, & Rodriguez, 1995; Addington, Stephens, Widdicombe, & Rekab, 2005; Davies, 2016; Miles, Zeng, McLauchlan, & Huckabee, 2013; Nakajoh et al., 2000; Nakazawa, Sekizawa, Ujiie, Sasaki, & Takishima, 1993; Sekizawa, Ujiie, Itabashi, Sasaki, & Takishima, 1990; Wakasugi et al., 2008; Yamanda et al., 2008).

1.6.2 Methods of Cough Reflex Testing

Over the last few decades, a range of methods has been used to test cough (Davies, 2016; Irwin et al., 2006; A. C. Miles, 2013; Morice et al., 2007; Morice, J. A. Kastelik, & R. Thompson, 2001; Pecova, Javorkova, Kudlicka, & Tatar, 2007; Redington, Morice, & Kastelik, 2005). Varying tools, including nebulisers and delivery sets, tussigens, methods and outcome measures, mean it is often impossible to compare studies or reproduce results and incorrect conclusions may be drawn. Published reviews of cough testing literature have strongly recommended standardisation of methods in future research (Irwin et al., 2006; Morice et al., 2007; Morice et al., 2001; Pecova et al., 2007; Redington et al., 2005).

In 2007, Morice and colleagues published a set of guidelines on the assessment of cough to address the variability of definitions and methodology in the literature. Two of the authors' primary goals were to establish "safe, standardised methods of inhalation cough challenge" and to promote "reliable, reproducible and relevant clinical cough recording and analysis" (p. 1257). The authors recommended that cough be defined in basic scientific articles as a "three phase motor act", consisting of an inspiratory phase, compressive phase and expulsive phase (Morice et al., 2007). Morices's recommendations and additional

assessment guidelines provide a standardised baseline for cough researches to use in study design and reporting.

1.6.2.1 Tussigens

The cough reflex can be stimulated mechanically or chemically and both methods are used to test the cough reflex. Mechanical stimulation can be performed during VES by ejecting a burst of air or water at the vocal folds or laryngeal mucosa and observing for a response (Aviv et al., 1998; Tanaka et al., 2005). Tanaka and colleagues (2005) used this method to test cough sensitivity in patients who had undergone simple surgery when comparing the impact of LMA in comparison to traditional endotracheal tubes. Sensory testing during videoendoscopy allows the clinician to listen for a cough response and observe the movements of the vocal cords during cough and other reflexes, including the glottic closure and the expiration reflex (Aviv et al., 1998). Together, these observations give the clinician an indication of an individual's sensory integrity. However, the equipment required to perform this type of testing is expensive and requires a high level of skill. Therefore, while VES with sensory testing is useful for instrumental assessment, it is not ideal as a screening tool for cough sensitivity.

Capsaicin is a non-acid chemical tussigen derived from red pepper that is frequently used in cough research and known to stimulate urge-related coughing through activation of C-fibers (Fujimura et al., 1995; Pecova et al., 2007). It has little to no effect on mechanoreceptors (Canning, 2006; Mazzone et al., 2005; J. Widdicombe, 2001). Cough is reliably stimulated by inhaled nebulised capsaicin with a good reproducibility. However, tachyphylaxis occurs with repeated trials and recovery to baseline sensitivity can take more than three hours (Morice, Higgins, & Yeo, 1992; Pecova et al., 2007). Also, capsaicin stimulation, through its activation of chemoreceptors, may have little effect on elicitation of the "true" cough reflex (Canning, 2006).

Tartaric acid and citric acid are the most commonly used acid tussigens (Bickerman & Barach, 1954; Morice et al., 2001). Addington, and colleagues (Addington et al., 1998; Addington & Stephens, 1999; Addington, Stephens, Gilliland & Rodriguez, 1999; Addington, Stephens & Gilliland, 1999; Addington, Stephens & Goulding, 1999; Addington et al., 2005) have used tartaric acid in a series of studies looking at cough reflex and pneumonia after stroke, but did not provide a justification for the choice of tussigen. There is little normative data for tartaric acid and studies suggest cough reflex testing with tartaric acid is not as reproducible as with citric acid (Morice et al., 2001).

Citric acid is the most commonly used acid tussigen in cough physiology studies (Morice et al., 2001). Unlike capsaicin, citric acid stimulates the mechanoreceptors as well as chemoreceptors (Wong, Matai, & Morice, 1999), provoking both a reflexive cough as well as an urge-to-cough. Although citric acid stimulates receptors throughout the larynx, trachea and lungs (Wong et al., 1999), citric-acid sensitive receptors appear to be more dominant in the larynx. This is in contrast to the capsaicin receptors, which are more common in the peripheral airways (Hansson, Wollmer, Dahlback, & Karlsson, 1992; Morice, 1996). This is important as the receptors of the larynx are crucial in triggering cough to protect the airway from the aspiration of food and fluids (Morice et al., 2007).

Cough testing with citric acid is reproducible and, although tachyphylaxis does occur, recovery to baseline sensitivity following repeated testing occurs more quickly with citric acid than capsaicin (Morice et al., 1992). This makes it the preferred tussigen for repeated cough measures, such as the dose response method, when increasing doses of the tussigen are delivered until a threshold is established (Morice et al., 2007). A one-minute break is recommended between trials to reduce the influence of tachyphylaxis (Morice et al., 2007). An added benefit of citric acid is its safety and record of subject tolerance; in more than 60 years of use there have been no recorded serious adverse reactions in response to citric acid.

1.6.2.1.1 Preparation of citric acid

There is very little published research to offer guidance on the preparation of citric acid. In the ERS Guidelines on the Assessment of Cough, Morice and colleagues (2007) recommend storing a stock solution of 3.0 mol citric acid in sterile 0.9% saline solution and creating dilutions to the desired test concentrations daily. This is to ensure a consistent concentration of citric acid is delivered each time, as stability of the solution is essential for valid CRT results. In addition, The United States Food and Drug Administration (2002) recommends that all inhalation solutions be sterile due to the risk of infection caused by inhaling nebulised solutions contaminated with bacteria (Hovig, 1981; Reinartz, Pierce, Mays, & Sanford, 1965). However, daily preparation of citric acid in a sterile environment is expensive, time consuming and prohibitive to use in a clinical setting.

Falconer and colleagues (2014) established a guideline for best practice in the preparation and use of citric acid to address these issues. Sterility testing revealed that citric acid was inhospitable to common bacteria with experimentally introduced staphylococcus aureus surviving for a maximum of 40 minutes. However, introduced candida albicans survives in citric acid. Therefore, there is a risk of cross-contamination when using a single bulk solution of citric acid solution between multiple patients. Stability testing determined that citric acid solution is stable for a minimum of 28 days. The authors suggested that citric acid be prepared aseptically every 28 days and stored in single use syringes to eliminate the risks of cross-contamination and degradation of the solution. These guidelines allow citric acid to be prepared in the hospital setting safely and at minimal cost.

1.6.2.2 Delivery methods

There are two primary methods of citric acid delivery during dose response cough reflex testing: single vital-capacity breaths and tidal breath inhalation (Morice et al., 2007). In the single vital-capacity breath approach, the participant's nose is occluded and they are

instructed to take a single, quick breath through a mouthpiece (Addington, Stephens, & Gilliland, 1999). The amount of tussigen may be controlled by a dosimeter to ensure that a predetermined amount is administered with each trial (Morice et al., 2007).

In the tidal breath inhalation method, participants inhale the nebulised tussigen through a facemask or mouthpiece for a period of time, usually 15 to 60 seconds, and the number of coughs is counted (Dicpinigaitis, 2007; Morice et al., 2007; Nejla, Fujimura, & Kamio, 2000; Redington et al., 2005; Wakasugi et al., 2008). Although some researchers have recommended the single-dose response method for accuracy and reproducibility (Dicpinigaitis, 2007; Morice et al., 2007), a comparison of the two methods produced good agreement (Nejla et al., 2000). Pecova and colleagues (2007) reported that fewer healthy participants coughed on citric acid trials compared to capsaicin trials when the patient was instructed to take a single, full breath. The authors warned that citric acid may not be as well suited for measuring decreased cough reflex sensitivity using the single vital capacity breath method. Therefore, tidal breath method may be more suitable to CRT with nebulised citric acid.

Addington and colleagues (1995) were the first to propose CRT as a tool for assessing risk of silent aspiration during swallowing. They utilised a mouthpiece for delivering the tussive agent, a method that has been replicated by many others (Lee, Kim, Seo, & Kang, 2014; Leow, Beckert, Anderson, & Huckabee, 2012; Wakasugi et al., 2014). However, the mouthpiece method has obvious drawbacks for any participant who has facial weakness or difficulty following commands, both of which are common among ICU patients. For these populations, delivering the tussigen via facemask may be more appropriate as it allows the participant to breathe passively. This method has been employed in a number of research studies for this reason (Monroe, Manco, Bennett, & Huckabee, 2014; Wakasugi et al., 2008). Figure 7 outlines the different cough testing methodology in use.

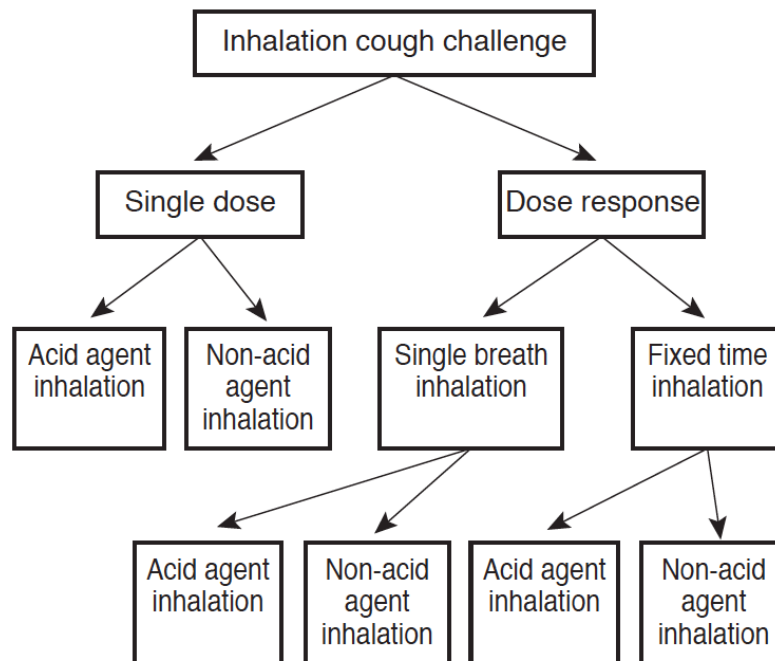


Figure 7. Different Methodology Used in CRT.

From “Cough challenge in the assessment of cough reflex,” by A. H. Morice, J. A. Kastelik, & R. Thompson, 2001, *British Journal of Clinical Pharmacology*, 52(4), p. 365-375. Copyright 2001 by John Wiley and Sons. Reprinted with permission.

1.6.2.3 Nebulisers

During CRT, tussigens are delivered by a nebuliser, which is a device that uses compressed air to convert a liquid solution into an aerosol. Jet nebulisers are usually used for CRT (Morice et al., 2007). They are small, easy to transport to the patient’s bedside and are ideal for use in ICU. The specifications of the nebuliser should be standardised across CRT trials as both the flow rate of the nebuliser and the droplet size produced can impact CRT results (Morice et al., 2007; Morice et al., 2001). When citric acid aerosol is inhaled, smaller particles are able to travel more distally in the airways. As a result, particles of 10µm or greater are deposited in the mouth and throat, 5 to 10µm between the throat and lungs and

particles less than 5µm are deposited most distally in the lungs (Morice, J. A. Kastelik, & R. Thompson, 2001). Because citric acid is thought to stimulate cough receptors that predominate in the larynx (Morice, 1996), particles between 5µm and 10µm may be ideal (Redington et al., 2005).

The flow rate varies widely across nebulisers (Terzano, Petroianni, Parola, & Ricci, 2007) and even within nebulisers (Morice et al., 2007). Nebulisers with a lower flow rate produce a greater cough response, possibly due to an association between lower flow rate and increased deposition in the larynx (Barros, Zammattio, & Rees, 1990). To strictly control the inspiratory flow rate, some experts suggest integrating a dosimeter into the nebuliser (Dicpinigaitis, 2007; Morice et al., 2007; Redington et al., 2005). Used with the single vital capacity breath method, the dosimeter releases a fixed amount of tussigen over a set period on inhalation (Redington et al., 2005).

1.6.2.4 Placebo

Humans can consciously suppress the urge to cough (Hegland, Bolser, & Davenport, 2012; Hutchings, Eccles, Smith, & Jawad, 1993; Lee, Cotterill-Jones, & Eccles, 2002) and coughing can occur in the absence of stimulus. Guinea pigs have been conditioned to cough to an odour by presenting the odour with a tussigen for several days and then withdrawing the tussigen, suggesting that the cough response can be learned (Pinto, Yanai, Sekizawa, Aikawa, & Sasaki, 1995). For this reason, the authors of the ERS Guidelines on the Assessment of Cough recommend that placebo trials with normal saline should be randomly interspersed between repeated trials of citric acid, as occurs in the dose-response method of testing (Morice et al., 2007).

1.6.2.5 Suppressed versus natural cough

Cough testing can employ either a natural or suppressed cough method. The ERS Guidelines on the Assessment of Cough recommend that subjects be clearly instructed not to

suppress cough, suggesting the instructions, “Allow yourself to cough if you need to and as much as you need to” (Morice et al., 2007). However, others suggest that the point at which cough can no longer be suppressed may represent the truer cough threshold as this is presumably the point at which the person has lost the ability to cortically override the brainstem cough response (Hegland et al., 2012; Monroe et al., 2014). Monroe and colleagues (2014) performed CRT with citric acid with 160 healthy volunteers who were split evenly between younger and older cohorts. Cough thresholds were established in both natural and suppressed cough conditions. The instructions to the participants performing suppressed cough were to, “Try to suppress the cough as much as you can” (Monroe et al., 2014). The researchers reported that suppressed cough thresholds were significantly higher than natural cough thresholds, supporting the argument that the suppressed cough threshold is a more accurate representation of the true cough reflex threshold.

1.6.3 Interpretation of CRT results

1.6.3.1 Norms

A benefit of citric acid use in cough testing is that normative values and intra- and inter-rater reliability have been established (Miles & Huckabee, 2013; Monroe et al., 2014). Monroe and colleagues performed cough threshold testing on 160 individuals equally split across age groups (younger ≤ 60 years, older ≥ 60 years) and gender. A DeVilbiss nebuliser with an unrestricted flow rate of 8 l/m was used to deliver citric acid aerosol via facemask using the tidal breath method. Both natural and suppressed cough methods were tested. Placebo trials were randomly interspersed with citric acid trials. The initial cohort of 80 patients underwent cough threshold testing with citric acid doses ranging from 0.8 to 2.6mol/l in increments of 0.2mol/L. However, at 0.8 mol/L, 92.5% of participants produced a natural and 70% produced a suppressed cough, indicating a flooring effect. Eighty more participants

were recruited and underwent testing with doses ranging from 0.1 to 1.2 mol/l (Monroe et al., 2014).

Eight (5%) participants did not produce a natural cough response at any concentration of citric acid. However, seven of these participants were in the second cohort, where the highest test concentration was 1.2mol/l. Presumably some participants would have triggered a cough at the higher concentrations tested in the first cohort. One (<1%) participant of the 80 tested did not produce a natural cough response at even the highest concentration of 2.6mol/l. Forty (22%) of the participants did not trigger a suppressed cough, but only 15 (19%) of them were tested at the higher concentrations. Certainly, this suggests that there is a very wide range of normal cough responses. Monroe and colleagues (2014) suggest considering the normal variation in cough sensitivity when evaluating the sensitivity and specificity of CRT. Of those participants who produced a cough, 97.3% had produced a natural cough by 1.6mol/l and 95.5% produced a suppressed cough by 1.2mol/l. The norms for both natural and suppressed cough appear in Figure 8. There is a significant peak at 0.8 mol/l, but some of these participants would have been from the first cohort and were not tested below 0.8mol/l, which is a clear limitation of the study (Monroe et al., 2014).

Miles and Huckabee (2013) reported fair to moderate inter- and intra-rater reliability amongst both experienced and inexperienced clinicians interpreting CRT result. Clinicians viewed videos of patients receiving a single dose of nebulised citric acid over 15 seconds, utilising a tidal breathing method via facemask. Clinicians were better at judging the presence or absence of cough than judging whether a cough response was strong or weak. It is interesting to note that the experienced clinicians overall inter- and intra-rater reliability was not significantly better than the inexperienced clinicians, despite eight hours of focused training and at least one year of experience using CRT.

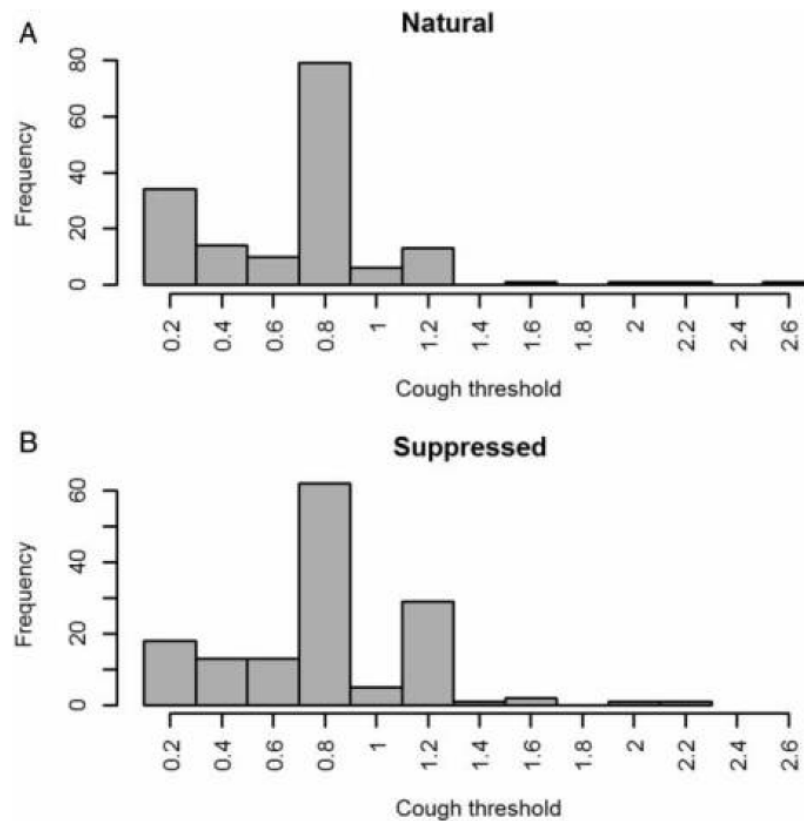


Figure 8. Natural and Suppressed Cough Thresholds in Healthy Volunteers.

From “Citric acid cough reflex test: establishing normative data,” by M. D. Monroe, K. Manco, R. Bennett, & M.-L. Huckabee, 2014, *Speech, Language & Hearing*, 17(4), p. 216-224. Copyright 2014 by Taylor & Francis Group. Reprinted with permission.

1.6.3.2 Factors Affecting Cough Sensitivity

Several factors can affect the cough reflex by either increasing or decreasing sensitivity (Redington et al., 2005). Many of these factors may be relevant to the ICU population and should be considered with interpretation of cough sensitivity in this population. Women have demonstrated increased sensitivity to tussigens (Becklake & Kauffmann, 1999; Dicipinigaitis & Rauf, 1998; Fujimura et al., 1996; Monroe et al., 2014; A. Morice, Kastelik, & Thompson, 2000). Smokers have reduced sensitivity to cough stimuli (Dicipinigaitis, 2003), although sensitivity improves almost immediately after quitting

smoking, then quickly returns to baseline when smoking is resumed (Sitkauskiene & Dicipinigaitis, 2010). Recent research by Dicipinigaitis, Chang, Dicipinigaitis and Negassa (2016) demonstrated reduced cough sensitivity in participants immediately after they smoked an e-cigarette containing nicotine, which was not seen after smoking a non-nicotine e-cigarette. The authors suggest the nicotine was responsible for blunting the cough response. This may indicate that the sensitivity of cough receptors is dynamic and subject to change in response to environmental conditions (Sitkauskiene, Stravinskaite, Sakalauskas, & Dicipinigaitis, 2007). Although adults have a less sensitive cough than children, natural cough thresholds appear to be stable throughout the adult years (Chang & Widdicombe, 2007). However, suppressed cough thresholds have been shown to be lower in elderly individuals (Leow et al., 2012). Gender, age and smoking status may be relevant to the cough sensitivity of individual patients in the ICU and, ideally, any study assessing the cough reflex in this population would capture these variables and consider their influence on CRT results. Smoking may be less relevant in the ICU post-extubation population as these patients have usually not been smoking recently due to illness, injury or smoking cessation prior to surgery, and the blunting effect of smoking on cough reflex appears to be short-lived.

Watando and colleagues (2004) randomised 60 hospital-level care patients into a control group or experimental group in a rigorously controlled study. At the outset of the study there were no significant differences in cough reflex threshold between the two groups. The experimental group received five minutes of teeth brushing after each meal in addition to weekly dental care. Cough reflex testing was repeated after 30 days of the oral care protocol and the experimental group demonstrated significantly lower cough reflex thresholds than the control group. These results suggest that cough reflex sensitivity may improve following intensive oral care. The authors did not provide an explanation for the mechanisms behind this effect and it is unclear if it was the reduction in oral bacteria or the stimulation to the oral

cavity that led to the change in cough reflex sensitivity. Davies (2016) quantified the oral bacteria of 102 acute stroke patients with dysphagia at admission to hospital, discharge from the acute stroke ward and one month following stroke and compared bacteria counts to results of CRT performed at the same time points. The author reported no significant relationship between bacteria counts and cough sensitivity, but suggested this may be due to an underpowered study. Orotracheally-intubated patients are not generally able to perform their own oral cares and the presence of the endotracheal tube can restrict access to the mouth. As a result, the oral cavities of these patients are likely to have high bacteria counts. The endotracheal tube can become covered in a bacterial film and provides a conduit from the mouth to the lungs (Scannapieco, 2006). Considering the volume of oral bacteria in the ICU population and its potential effect on cough reflex sensitivity, it should be considered as a factor in future studies evaluating dysphagia, aspiration and cough reflex in the ICU population.

Finally, cough reflex sensitivity has been reported to change over the course of a day, with stronger concentrations of citric acid required to stimulate cough in healthy volunteers in the afternoon (Pounsford & Saunders, 1985). Therefore, it has been recommended that repeated cough testing within an individual be repeated at similar times of the day (Pounsford & Saunders, 1985). However, in a study by Davies (2016), healthy volunteers underwent CRT using the tidal breathing method in the morning and afternoon and the author reported no significant difference in the cough sensitivity. Participants in the study by Davies (2016) brushed their teeth prior to CRT to reduce the potential impact of oral bacteria on cough sensitivity. These results indicate that time of testing may not be an important factor when performing CRT using a tidal breathing method.

1.6.4 Opioids

Because opioids are used so frequently in the ICU population, particularly in the period immediately following extubation (Elliott et al., 2013; Shehabi et al., 2013), the effect of opioids on the cough reflex deserves special attention. In 2013, researchers from 41 ICUs reviewed 569 admitted patients over a four-hour period (Elliott et al., 2013). Sixty percent of the participants were receiving either an analgesic or sedative on the day of the study; 61% of participants were receiving bolus dose of morphine or fentanyl and 46% of participants were receiving one or the other intravenously. The link between opioid use and cough has been well established for more than a century (Chung & Chang, 2002; Fantus, 1912) and opioids are reported to reduce cough sensitivity to citric acid (Kelly, Shaw, Brett, Greenwood, & Huckabee, 2016).

In a study by Morice and colleagues (2007), 27 participants with chronic cough were enrolled in a double blind, placebo-controlled crossover study evaluating the treatment effect of the opioid morphine. Participants in the experimental group received a 5mg dose of oral slow-release morphine twice per day and reported a rapid and significant improvement in quality of life ratings. The authors reported that treatment with morphine did not respond to a change in sensitivity to CRT with citric acid. It is possible that this is because the morphine reduced the cortically modulated urge-to-cough, but did not effect the reflexive cough triggered by citric acid. However, it is likely that the dose the authors used was below that needed to attenuate cough. Typical opioid doses in ICU are much higher than those Morice and colleagues (2007) studied. For example, ICU patients are routinely able to administer their own pain relief post-operatively via a syringe driver that delivers limited doses, most commonly one milligram of morphine every 5 minutes (McNicol, Ferguson, & Hudcova, 2015), compared to the 10mg over 24 hours used by Morice and colleagues (2007).

Kelly and colleagues (2016) examined the effect of more powerful doses of fentanyl on suppressed cough thresholds to citric acid. Thirteen healthy volunteers each received four

consecutive doses of 0.5µg/kg intravenous fentanyl, each five minutes apart. The mean of the participants' weights was 71.5kg, making the mean dose of fentanyl 35.8µg per dose for a mean total of 143µg. This is equivalent to 3.6mg of morphine per dose and a total dose of 14.3mg morphine (10µg fentanyl = 1mg morphine). The authors selected this dose to be representative of what a patient would receive perioperatively. Participants' cough reflex thresholds consistently rose over the course of the administration, from a mean of 0.51mol/l to 1.26mol/l after the final dose. Thresholds subsequently fell in the period after fentanyl administration, returning to a baseline in a mean of 44.6 (SD=18.8) minutes. These results clearly demonstrate that the use of opioids is a factor in cough testing and, as such, should be carefully considered in the interpretation of results. Neither Morice and colleagues (2007) nor Kelly and colleagues (2016) mention if gender made a difference in cough sensitivity to opioids, but others have reported that opioids have a significantly greater dampening effect on women's coughing when emerging from surgery when compared to male counterparts (Soh, Park, Kang, Lee, & Lee, 2014). This is likely due to women's increased sensitivity to opioids (Lee & Ho, 2013) and may further complicate the understanding of opioid effect on the cough reflex.

1.6.4.1 Measuring cough presence

When evaluating presence of the cough reflex, the most common method is to measure the concentration of tussive that is required to stimulate at least two coughs within 15 seconds (Dicpinigaitis, 2007; Miles, Zeng, et al., 2013; Monroe, Huckabee, & Robb, 2010; Wakasugi et al., 2008). The ERS recommends that researchers use either a C2 (the concentration of citric acid causing 2 coughs in 15 seconds) or C5 (the concentration of citric acid causing 5 coughs in 15 seconds) (Morice et al., 2007). The normative data of cough response to citric acid by Monroe and colleagues (2014) utilised the C2 method and,

therefore, selecting this method of recording CRT response offers the substantial benefit of being able to compare results to established norms.

Miles, Zeng and colleagues (2013) added a subjective assessment of cough strength to their cough reflex testing protocol. If C2 was present it was classified as either strong or weak, a judgement that the authors report has moderate reliability in untrained clinicians (Miles & Huckabee, 2013). They define weak cough as, “a cough that does not appear strong enough to clear aspiration and is substantially weaker than their own reflexive cough” (Miles, Moore, et al., 2013). The authors hypothesized that individuals with weak cough may be at increased risk of pneumonia because, despite having a cough response, they may still be unable to adequately clear aspirated material (Miles, Zeng, et al., 2013). Many patients in the ICU have a weak cough due to, but not limited to, supine positioning (Badr, Elkins, & Ellis, 2002), pain following surgery (Weissman, 1999) or weakness (De Jonghe et al., 2007), and judging cough strength may be beneficial in this group.

1.6.5 Cough Reflex Testing Application in Dysphagia

Addington and colleagues first proposed the application of CRT to the field of dysphagia in 1995. The authors initially suggested a two-part swallowing exam assessing the oral and pharyngeal phases of the swallow. The authors evaluated the oral phase of a participant's swallowing by assessing their ability to perform an oral hold task. Participants also underwent CRT using nebulised tartaric acid to determine the motor and sensory function of the internal branch of the SLN; performance on this task was used to assess the pharyngeal phase of swallowing. Participants with a strong cough and ability to hold 30ml of water in their mouth for 15 seconds were significantly less likely to aspirate or penetrate on VFSS ($p<.0001$). It is worth noting that the assessment proposed by the authors did not evaluate physiology of the oral transit or pharyngeal phases of swallowing and focused purely on airway sensation. Intact function of the SLN is vital in swallowing, but represents

only a portion of the sensory input and motor output that occurs during the pharyngeal phase of swallowing. This study marked the beginning of a series of research studies on CRT and swallowing by Addington and colleagues.

The subsequent study further developed CRT (Addington, Stephens, & Gilliland, 1999). One hundred and sixty-one stroke patients in a rehabilitation hospital underwent CRT and their cough responses were judged to be normal (strong) or abnormal (weak or absent). The primary outcome measure of interest was development of pneumonia. Only 78 participants underwent VFSS. One hundred and thirty-one (81%) participants had a normal cough response and none of these participants developed pneumonia, while of the 30 (19%) participants with abnormal cough, 5 (17%) developed pneumonia. Interestingly, this is a pneumonia rate of only 3%, which is well below reported pneumonia rates in the rehabilitation setting (Martino et al., 2005).

There are a number of other issues with the methods the authors employed. Participants who could not follow verbal commands or who had supplemental oxygen were excluded from the study. In addition, results were not considered valid if the participant could not form a sufficient seal around the mouthpiece. These criteria likely excluded patients with more severe strokes from participating, thus reducing the pneumonia rate amongst participants. There is also no indication of the time periods over which development of pneumonia was assessed or what criteria were used to determine a diagnosis of pneumonia. If pneumonia was only recorded in the acute stage it would result in a much lower rate than if patients were followed up for a period of time following their stroke. It is worth noting that the researchers did not consider cough effectiveness in the development of pneumonia by analysing differences between participants with strong or weak coughs, but just presence or absence of response. However, the correlation between abnormal cough reflex and development of pneumonia deserves further exploration.

Following this study, Addington, Stephens and Gilliland (1999) proposed a rigid assessment framework for clinical application of CRT (Figure 9), which they applied in a prospective study of 400 consecutive acute stroke patients. Participants in the experimental group who had an abnormal cough were managed conservatively, with no oral intake allowed. Participants with normal cough and ability to follow commands were progressed onto oral diets on the basis of a bedside exam. VFSS was only used to assess structural issues, such as fistula, but not to assess physiology of swallowing. The premise of this method was that CRT was able to rule out silent aspiration and patients with an intact reflexive cough could be correctly assessed through a clinical exam only. This approach does not, however, take into account the benefit of VFSS for identifying abnormal swallowing physiology and planning rehabilitation.

The primary outcome of the study was the development of pneumonia. Pneumonia rates in the experimental group, who received the CRT protocol, were compared to pneumonia rates in a control group at a sister hospital. Five (1%) of the 400 participants in the experimental group developed pneumonia compared to 27 (13%) of the 204 participants in the control group (Addington, Stephens, & Gilliland, 1999). When Addington, Stephens, Widdicombe & Rekab (2005) applied the same strict protocol to 818 consecutive acute stroke patients in a follow-up study, there was a significant difference in pneumonia rates for participants with normal versus abnormal CRT response ($p<.005$). The incidence of pneumonia was higher in participants with absent cough (15%) than weak cough (10%).

While these results are intriguing, there are significant limitations to these studies that should be considered when interpreting the results. The authors again excluded an unidentified number of participants who could not form a lip seal around the mouthpiece and who could not follow commands. As discussed previously, this would likely result in the more severe stroke patients being excluded, while no such exclusion occurred in the control

group. The choice by the authors to use patients at another hospital as the control introduced a number of potentially confounding variables. The differences in pneumonia rates between the two groups may be due to differences in the patient population or patient management rather than use of CRT. In addition, Addington, Stephens & Gilliland (1999) do not justify their decision to use tartaric acid and do not refer to normative data or explain the choice of concentration. Because cough sensitivity varies widely within individuals it is beneficial to have normative data to determine concentration selection and to compare results.

NORMAL Cough (Involuntary cough elicited on inhalation)

Cognition Adequate (able to follow commands or compensatory strategies):

Low risk of significant aspiration.

Feed according to results of bedside examination.

Cognition Diminished (cannot follow commands or compensatory strategies):

May have low risk of significant aspiration; feed according to results of bedside examination.

Compensatory feeding strategies, eg, PEG, may be considered.

Routine reassessment.

ABNORMAL Cough (Absent or weak involuntary cough on inhalation)

High risk of significant aspiration. Patient is at risk of developing pneumonia.

Consider restricted diet or NPO. Compensatory feeding strategies, eg, PEG, may be considered.

Routine reassessment.

Figure 9. Algorithm of Addington and Colleagues' Reflex Cough Test.

From “Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke,” by W. R. Addington, R. E. Stephens, K. Gilliland, & M. Rodriguez, 1999, *Archives of Physical Medicine and Rehabilitation*, 80(2), p. 150-154. Copyright 1999 by Elsevier.

Wakasugi and colleagues (Wakasugi et al., 2008) were the first to validate CRT with citric acid. Two hundred and four participants who had been referred for VFSS or VES for suspected dysphagia underwent CRT 1% weight/volume nebulised citric acid presented via facemask (with a nose clip) for one minute. A response of five or more coughs during the minute was considered a normal response while a response of four or fewer coughs was considered abnormal. CRT outcome was compared to VFSS or VES. When participants who

silently aspirated a trace amount were grouped with participants who did not silently aspirate, CRT had a sensitivity of 0.87 and a specificity of 0.89 for predicting silent aspiration. In 2014, the authors repeated the study but used a handheld nebuliser to deliver the citric acid. Sensitivity and specificity of CRT to predict silent aspiration was 0.86 and specificity 0.71. The authors did not clearly justify their choice of concentration, but all participants underwent instrumental assessment and their inclusion criteria and methodology were more likely to capture participants with severe dysphagia than those of the studies by Addington, Stephens, Gilliland & Rodriguez (1999) and Addington, Stephens & Gilliland (1999).

Miles and colleagues furthered understanding of CRT as a tool for detecting silent aspiration risk in two important studies. The first looked at the effect of CRT use on pneumonia rates, specifically in the stroke population (Miles, Zeng, et al., 2013). Three hundred and eleven consecutive stroke patients who had been referred to SLT were enrolled and randomised to a control group, who received a standard clinical examination, or an experimental group who received a standard clinical examination plus CRT. Standard clinical examination included a case history, cognitive/communication screen, cranial nerve assessment and observation of ingestion of food and fluids. Citric acid in concentrations of 0.8mol/L and 1.2 mol/L were delivered via tidal breathing with a facemask. Concentrations were selected based on the normative data from Monroe and colleagues (2014); normative data for concentrations below 0.8mol/L were not available at the time Miles, Zeng and colleagues (2013) completed their study. Natural and suppressed cough were assessed at 0.8mol/L, with two coughs on two out of three trials considered a positive response. If suppressed cough was absent it was retested at 1.2mol/L. Clinicians were advised to consider CRT results when making management decisions, but there was no prescribed protocol as in the studies by Addington Stephens, Gilliland & Rodriguez (1999) and Addington, Stephens & Gilliland (1999). Patients with an abnormal response to CRT were referred for VFSS more

often than their counterparts with an intact cough, suggesting there was some change in clinician behaviour. However, referral rates for VFSS were still low. Participants who failed CRT, developed pneumonia and underwent instrumental assessment were all referred for instrumental assessment before the development of pneumonia. Participants who passed CRT or who didn't undergo CRT were only referred for instrumental assessment after they developed pneumonia. This suggests an over-reliance by clinicians on a failed CRT result to refer for instrumental assessment.

Addition of CRT to usual clinical practice was not enough to influence patient outcomes and the authors reported no significant differences in pneumonia rates between the control and experimental groups (21% and 26% respectively), mortality rates or length of stay. The authors suggest that a more rigid management protocol, similar to the one used by Addington Stephens, Gilliland & Rodriguez (1999) and Addington, Stephens & Gilliland (1999), may be necessary to reduce pneumonia rates. Strengths of this study include randomisation to experimental and control groups, adherence to the ERS Guidelines on the Assessment of Cough (Morice et al., 2007), clear documentation of methodology and use of normative values for CRT response.

In response to the suggestion of Miles, Zeng and colleagues (2013) that a more rigid management protocol may have influenced patient outcomes, Davies (2016) compared outcomes of participants who were managed under such a protocol to the outcomes of Miles, Zeng and colleagues' (2013) experimental group, who were managed with CRT, but no strict protocol dictating management. Two hundred and eighty four acute stroke patients underwent CRT prior to initiating oral intake. Participants who produced a strong cough response to 0.8 mol/L nebulised citric acid and could not suppress cough at 0.8 or 1.2 mol/L were considered to have passed CRT. Decisions regarding intake for these participants were based on clinical assessment by an SLT, which included oral trials of food and liquid. Participants who failed

CRT were kept nil by mouth until VFSS and then progressed to oral intake only if they did not aspirate on VFSS or aspirated with a cough response. The author reported a significantly lower rate of aspiration pneumonia in the protocol group, with a pneumonia rate of 10% in this group compared to a rate of 28% in the historical group. The odds of developing aspiration pneumonia were 3.24 times greater if no protocol were used. There are some limitations to this study, most notably the use of an unmatched historical control group, but the results suggest that the implementation of a strict management protocol incorporating CRT can have a powerful effect on patient outcomes.

Miles, Moore and colleagues (2013) also conducted a validity study comparing CRT results to instrumental assessment. A total of 181 patients referred for assessment underwent CRT and either VFSS or VES within one hour. Threshold testing was performed with citric acid doses of 0.4mol/L, 0.6mol/L and 0.8mol/L. Placebo doses were interspersed between each concentration change. Presentation methods were the same as the previous study (Miles, Zeng, et al., 2013), but only natural cough was assessed. Cough was judged to be present (two or more coughs on at least two of three trials) or absent (fewer than two coughs on two or more trials), then strong or weak, as defined previously. VFSS and VES were performed according to standard protocols. There was almost perfect inter-rater agreement on PAS scores at 98% for VES and 96% for VFSS. There was also almost perfect inter-rater agreement for judging aspiration response at 97%. There was a significant association between CRT response and cough response to aspiration when weak cough responses to CRT were grouped with strong responses, with the odds of silent aspiration increasing as cough thresholds increased. Sensitivity and specificity were calculated for each concentration and were optimised at 0.6mol/L for VFSS (71% and 60% respectively) and 0.4mol/L for VES (69% and 71% respectively). This study by Miles, Moore and colleagues (2013) was the first to compare CRT threshold testing to instrumental assessment. Again, the authors followed

the ERS Guidelines on the Assessment of Cough (Morice et al., 2007) and carefully outlined and justified their methodology. These steps make it possible to compare results between studies.

Both sensitivity and specificity were lower than that reported by Wakasugi and colleagues (2008). The lower specificity is likely because of the lower concentrations of citric acid used by Miles, Moore and colleagues (2013). The authors reported increasing sensitivity and decreasing specificity as the concentration of citric acid increased. Participants with an intact cough reflex are less likely to fail as the strength of the tussive increases, resulting in greater sensitivity. However, higher concentrations of citric acid may be more likely to trigger cough in patients with an abnormal cough reflex, and a drop is seen in specificity with higher doses (Miles, Moore, et al., 2013). Grouping weak responses with absent responses improved sensitivity but caused a large drop in specificity. A limitation of the study is the slight differences in methodology between the VES and VFSS groups, which prevented the data being pooled. This study makes a solid attempt at validating CRT in a general population and the data suggest that CRT is a useful addition to a standard clinical evaluation.

1.6.6 Summary

CRT has shown promise in a number of clinical studies as a useful tool for identifying patients who are at risk of silent aspiration, particularly in the elderly or neurologically impaired populations. Given the prevalence of silent aspiration in the ICU post-extubation population and lack of standard screening and assessment tools, CRT could be a useful addition to this setting. To date, researchers evaluating the usefulness of CRT have employed a wide range of methodologies, making it difficult to compare or replicate results. Cough reflex testing with citric acid offers a number of benefits: it is safe, reproducible, results in less tachyphaxis than other tussive agents and has established preparation guidelines and

normative data available. In line with the ERS Guidelines on the Assessment of Cough, which advise that standardised research methods should be developed (Morice et al., 2007), it would be advisable to use the same methods as the studies that established the normative data, which the authors developed to be in line with the ERS recommendations. Therefore, further CRT research with citric acid should use the dose-response method with tidal breathing via facemask and cough should be measured by the C2 standard. In addition, placebos should be randomly interspersed with citric acid trials. There are a couple of considerations unique to the ICU population. The effect of opioids on cough could be a confounding factor when assessing cough reflex in this population and should be carefully considered. Opioids do impact cough sensitivity and make it difficult to determine the cause of cough impairment, but this is less important when assessing the impact of absent cough reflex on swallowing. Absent cough reflex may place an individual at risk of silent aspiration regardless of the cause. Also, many ICU patients are likely to have a weak cough, and this should be taken into account with performing CRT.

1.7 *Problem and Hypothesis*

1.7.1 *Statement of Problem*

Aspiration, often silent, is a frequent occurrence in intensive care patients after orotracheal extubation, although little is known about the effect of short-term intubation on swallowing and airway protection. Currently there is no standardly accepted screening tool or assessment protocol for the post-extubation population. The cough reflex is an important mechanism for protecting the airway against aspiration. There is some evidence that orotracheal intubation adversely affects cough reflex, but there are no clear data on the prevalence or duration of absent cough reflex post-extubation. CRT has shown promising results in other patient populations and may be a valid screening tool for identifying those ICU patients who are at the greatest risk of silent aspiration after extubation.

1.7.2 *Aims*

- To determine the prevalence of absent cough reflex in ICU patients after extubation
- To determine the time from extubation to return of the cough reflex
- To determine the prevalence of aspiration - silent and overt - following extubation in patients with short-term (<48 hours) and prolonged (>48 hours) intubation
- To determine the validity of CRT for identifying which patients are most likely to silently aspirate post-extubation

1.7.3 *Significance of Research*

The following studies will, for the first time, directly investigate the effect of orotracheal intubation on the cough reflex. The results of these studies will provide necessary data on the effect of short-term and prolonged intubation on the cough reflex and swallowing. These studies will provide guidance to the multidisciplinary team caring for ICU patients who have been orotracheally intubated.

1.7.4 *Question 1: Does Orotracheal Intubation Affect Cough Response?*

1.7.4.1 Hypotheses:

- There is a significant decrease in sensitivity to CRT immediately following extubation in neurologically intact adults undergoing elective cardiac surgery.
- In participants with an impaired cough reflex, cough response returns to baseline sensitivity by discharge from hospital.

1.7.4.2 Rationale:

Dysphagia and aspiration after orotracheal intubation in the ICU population are frequently reported in the literature across a variety of populations (Ajemian et al., 2001; El Solh et al., 2003; Hafner et al., 2008; Macht et al., 2011; Noordally et al., 2011; Scheel et al.,

2016). Studies measuring frequency of aspiration in a general ICU population post-extubation indicate that it occurs in up to 58% of patients (Scheel et al., 2016). Intensive care patients who aspirate are at increased risk of developing nosocomial pneumonia (Safdar et al., 2005), which is the most common infection in ICU and can result in increased length of stay, mortality and cost of care (Safdar et al., 2005).

Recently extubated intensive care patients are particularly at risk of silent aspiration, which cannot be reliably identified by bedside clinical assessment (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). Studies utilising instrumental assessment in this population have reported prevalence of silent aspiration ranging from 8% to 25% (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). Often these patients are allowed to eat and drink soon after extubation, potentially putting them at increased risk of aspiration and subsequent pneumonia.

Sensory testing of patients after orotracheal intubation suggests that airway reflexes are impaired in these patients in the short and medium term (Colice et al., 1989; Tanaka et al., 2005). Airway sensation in the recently extubated population has been tested by injection of water into the glottis (Tanaka et al., 2005), presence of a gag on laryngoscopy (Colice et al., 1989), and light touch to the aryepiglottic folds using a laryngoscope (Scheel et al., 2016).

CRT is emerging as a useful tool for testing subjects' ability to protect their airway through reflexive cough (Addington et al., 2005; Wakasugi et al., 2008). Sensory testing with CRT is preferable to the methods above because there are established norms (Monroe et al., 2014) and guidelines for CRT use (Morice et al., 2007). Currently, there is no evidence in the literature describing the use of CRT to test sensation after extubation. Most research relating cough reflex to safety during swallowing has been in the stroke population. Absent cough to CRT with acidic tussives (i.e. citric acid and tartaric acid) has been reported to have a high

specificity as a predictor of aspiration pneumonia (Addington et al., 2005; Wakasugi et al., 2008). Research by Miles, Zeng and colleagues (2013) demonstrated a non-significant trend for increased in mortality in patients with absent cough reflex. In addition, Miles and colleagues (Miles, Moore, et al., 2013) reported a significant association between absent response to CRT and silent aspiration on instrumental assessment in patients referred for instrumental assessment with a range of diagnoses.

Given that aspiration places ICU patients at risk of pneumonia, silent aspiration is common in patients after extubation and CRT testing is a useful tool for determining risk of silent aspiration, it follows that it may be useful to use CRT with patients after orotracheal extubation to screen for risk of silent aspiration. However, it is not currently known if the cough reflex is routinely impaired after orotracheal extubation. This research study will test the hypothesis that orotracheal intubation inhibits cough response to nebulised citric acid in neurologically intact adults undergoing intubation for elective cardiac surgery. It will also aim to determine when, in 12-hour intervals, most subjects' cough response returns to pre-intubation baseline.

1.7.5 Question 2. Is CRT result an accurate predictor of silent aspiration on VES and, if so, which concentration of citric acid provides the best predictive measure?

1.7.5.1 Hypotheses:

- There is a significant decrease in sensitivity to CRT within 24 hours following extubation.
- There is a significant correlation between CRT results and the presence or absence of silent aspiration on videoendoscopy.

1.7.5.2 Rationale:

Dysphagia and aspiration after orotracheal intubation in the ICU population are frequently reported in the literature across a variety of populations (Ajemian et al., 2001; El Solh et al., 2003; Hafner et al., 2008; Macht et al., 2011; Noordally et al., 2011; Scheel et al., 2016). Studies measuring frequency of aspiration in a general ICU population post-extubation indicate that it occurs in up to 58% of patients (Scheel et al., 2016). Intensive care patients who aspirate are at increased risk of developing nosocomial pneumonia (Safdar et al., 2005), which is the most common infection in ICU and can result in increased length of stay, mortality and cost of care (Safdar et al., 2005).

Recently extubated intensive care patients are particularly at risk of silent aspiration, which cannot be reliably identified by bedside clinical assessment (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). Studies utilising instrumental assessment in this population have reported prevalence of silent aspiration ranging from 8% to 25% (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). Often these patients are allowed to eat and drink soon after extubation, potentially putting them at increased risk of aspiration and consequent chest infection.

Sensory testing of patients after orotracheal intubation suggests that airway reflexes are impaired in these patients in the short- and medium-term (Colice et al., 1989; Tanaka et al., 2005). Airway sensation in the recently extubated population has been tested by injection of water into the glottis (Tanaka et al., 2005), presence of a gag on laryngoscopy (Colice et al., 1989), and light touch to the aryepiglottic folds using a laryngoscope (Scheel et al., 2016).

CRT is emerging as a useful tool for testing subjects' ability to protect their airway through reflexive cough (Addington et al., 2005; Wakasugi et al., 2008). Sensory testing with CRT is preferable to the methods above because there are established norms (Monroe et al.,

2014) and guidelines for CRT use (Morice et al., 2007). Currently, there is no evidence in the literature describing the use of CRT to test sensation after extubation. Most research relating cough reflex to safety during swallowing has been in the stroke population. Absent cough to CRT with acidic tussives (i.e. citric acid and tartaric acid) has been reported to have a high specificity as a predictor of aspiration pneumonia (Addington et al., 2005; Wakasugi et al., 2008). Research by Miles, Zeng and colleagues (2013) demonstrated a non-significant trend for increased mortality in patients with absent cough reflex. In addition, Miles, Moore and colleagues (2013) reported a significant association between absent response to CRT and silent aspiration on instrumental assessment in patients referred for instrumental assessment with a range of diagnoses.

Given that aspiration places ICU patients at risk of pneumonia, silent aspiration is common in patients after orotracheal extubation and CRT testing is a useful tool for determining risk of silent aspiration, it follows that it may be useful to use CRT with patients after orotracheal extubation to screen for risk of silent aspiration. However, it is not currently known if absent cough to CRT is a valid predictor of silent aspiration in this population. Cough impairment in this population may occur as a result of laryngeal trauma or damage to the recurrent laryngeal nerve, which makes this group unique to other populations with dysphagia. It is important to validate CRT in this unique population. This study aims to do this as well as to determine the prevalence of cough reflex impairment in ICU patients following orotracheal extubation.

PART B: ORIGINAL RESEARCH

CHAPTER TWO

Study I

2 Study I: Recovery of Cough Following Extubation after Coronary Artery Bypass Grafting: A Prospective Study

2.1 Study Objectives

2.1.1 Primary Objective

To test the hypothesis that there is a significant decrease in sensitivity to CRT immediately following extubation in neurologically intact adults undergoing elective cardiac surgery

2.1.2 Secondary Objective

To determine when, in 12-hour intervals, cough response returns to pre-intubation baseline.

2.2 Material and Methods

2.2.1 Participants

Patients greater than 18 years of age and scheduled for elective CABG at the study hospital were eligible for inclusion in the study. Patients having valve surgery alone or valve surgery with CABG, or those with a history of dysphagia, head and neck cancer or neurological disease were excluded. The study size was chosen to give 90% power with a measurement error of +/- 10% to estimate the proportion of patients whose cough reflex had diminished (Stata/IC 11.2, StataCorp LP, Texas, USA). All participants were placed on cardiopulmonary bypass for their surgery and received opioids as part of their initial anaesthetic and for analgesia during the follow-up period.

2.2.2 Procedures

Each participant was enrolled prior to surgery. At the time of enrolment, CRT, as described below, was performed to establish each participant's baseline threshold for reflexive cough (CRT1). When each participant was extubated following surgery, the ICU nurse notified the researcher who then performed the first follow-up assessment (CRT2) within two hours of extubation. Each participant that failed CRT2 was further evaluated each morning between 0700 and 0900 and each evening between 1900 and 2100. Testing was continued until each participant's cough was judged to be at their CRT1 level, they were discharged from hospital, they withdrew or they died. Follow-up testing was performed in ICU and on the cardiothoracic unit. In addition to CRT results and demographic information, anaesthetic and surgical details (endotracheal tube size, airway intubation grade, time on bypass) and information regarding on-going treatment (length of intubation, ICU discharge date, discharge destination, Acute Physiology & Chronic Health Evaluation III [APACHEIII] scores and opioid type and dose) were gathered from the medical record.

2.2.2.1 Cough Reflex Testing

Five millilitre syringes of sterile citric acid diluted in 0.9% sodium chloride were prepared in three concentrations: 0.4, 0.8 and 1.2 mol/L. These concentrations were chosen based on normative data which indicates that 95.5% of normal participants triggered suppressed cough at or below 1.2 mol/L while the mean for triggered suppressed cough for elders was 1.03 mol/L (Monroe et al., 2014). Citric acid solution was presented using a PulmoMate Compressor/Nebuliser (Model 4650I, DeVilbiss Healthcare LLC, Pennsylvania, USA) with a predetermined free-flow output of 8 L/min and a restricted flow output of 6.6 L/min.

The participant was seated upright to at least 60°. The lowest concentration of citric acid (0.4 mol/L) was presented first, followed by 0.8 and 1.2 mol/L as needed. Citric acid was delivered for 15 seconds and patients were instructed to "breathe normally and try not to

cough”. A suppressed cough method was chosen to guard against placebo cough and because it may represent a more accurate reflection of the true reflexive cough (Hegland et al., 2012). In addition, patients were reluctant to cough after cardiothoracic surgery and instinctively suppressed cough, so use of a suppressed cough method ensured consistency in pre- and post-intubation testing. Each concentration was presented up to three times with a minimum of 1 minute between each presentation to prevent tachyphylaxis (Morice et al., 2007). In this study, we define cough as a “forced expulsive manoeuvre or manoeuvres against a closed glottis that are associated with a characteristic sound or sounds”, which is consistent with ERS recommendations (Morice et al., 2007, p.1256). The cough reflex was considered present if the participant produced two or more audible successive coughs (C2) on two presentations of a single concentration. Saline trials were randomly interspersed with citric acid trials. If a participant coughed in response to a saline trial, a second saline trial was administered. If the participant coughed on two trials of saline, the cough response was considered abnormal and the participant excluded. Increasing concentrations were presented until the cough reflex threshold was identified or judged absent. During follow-up testing, the participant’s baseline threshold was the lowest concentration of citric acid that produced a C2 suppressed response.

2.2.2.2 Opioids

Opioids are known to suppress cough (Kamei, 1996). All patients were sedated peri- and post-operatively with propofol and only extubated once sedation had been ceased and they woke. All received opioids as part of their anaesthesia and for post-operative analgesia. The only opioids administered were morphine and fentanyl; morphine was avoided in patients with pre-existing or post-operative renal impairment. No other agents with known anti-tussive properties (e.g., lidocaine) were used with patients in the post-extubation period.

The morphine equivalent dose was calculated for each participant using ten micrograms fentanyl equals one milligram morphine. The total morphine equivalent dose administered from time of induction to final CRT was divided first by patient weight in kilograms then by the number of hours in this period to determine the administered mean morphine dose in milligrams per kilogram per hour (mg/kg/hr). Further analysis of opioid dose was completed on data from CRT2. Morphine equivalent dose in mg/kg/hr was again calculated for each participant, capturing only opioids administered intra-operatively and post-operatively up to completion of CRT2.

2.3 *Statistical Analysis*

The average time post-extubation of each follow-up and the percentage of participants with cough response present at baseline level at each follow-up were calculated. For the predictor variables, continuous variables were grouped into quartiles for analysis. Time to return of baseline cough response for each participant was plotted using the Kaplan-Meier survival curve. Log rank tests were performed to evaluate for significance between groups with an a priori significance level set at 0.05. A Mann-Whitney U test was performed to analyse the relationship between morphine equivalent dose and performance at CRT2 with an a priori significance level set at $p < 0.05$.

2.4 *Results*

Recruitment began in March 2013 and was completed in August 2013. During that period, a total of 104 patients met eligibility criteria of which 84 (68 male) consented to participation. Two participants were excluded because they did not cough at any concentration, therefore post-extubation reduction in cough could not be assessed. One participant was excluded from analysis because he did not regain consciousness following surgery and later died. Demographics of the participants who completed the study are

displayed in Table 2. The mean age of participants was 65 years (SD=8.45). Endotracheal tube size ranged from 7 to 9 and intubation grade was 1 in over half of the participants (n=48, 59%). Eighty percent (n=65) of participants were discharged directly home from hospital. One participant died after completing the study due to a new stroke. Time on bypass, length of intubation, morphine equivalent dose, APACHE III score and length of ICU stay are all summarised below.

Table 2. Participants' Baseline Characteristics

Total participants		n=81
Gender	Male	68 (84%)
	Female	13 (16%)
Age		Mdn=66, IQR=60,70
Tube size	7	3 (4%)
	8	61 (75%)
	9	17 (21%)
Intubation grade	1	48 (59%)
	2	27 (33%)
	3	3 (4%)
	Missing	3 (4%)
Discharge destination	Home	65 (80%)
	Other hospital	15 (19%)
	Died	1 (1%)
Time on Bypass		Mdn=93mins, IQR=74,111)
Length of intubation		Mdn=10.2hrs, IQR=8.75,13.3
Morphine dose (mg/kg/hr)		Mdn=0.175, IQR=0.088,1.14
APACHEIII score		Mdn=39, IQR=34,45
Length of ICU stay		Mdn=26hrs, IQR=23,46

At pre-surgery baseline test, CRT1, 73% (n=59) of participants had a positive cough response at 0.4 mol/L citric acid, 16% (n=13) at 0.8 mol/L and 11% (n=9) at 1.2 mol/L. All participants had absent cough to normal saline (100%). Two participants withdrew following surgery and did not undergo follow-up CRT. These participants were excluded from analysis.

A further 11 participants withdrew at various points across the study because they did not want to repeat CRT. The numbers of participants tested at each study point are outlined in Figure 10 below with numbers passing and failing CRT at their baseline level each follow-up.

Results of follow-up CRTs are displayed in Table 3 and a bar chart displaying the proportion of present and absent cough responses at baseline level at first follow-up, CRT2, through CRT6 is displayed in Figure 11. At CRT2, 60% of participants had an abnormal cough while 40% had a cough response present at baseline level. By CRT3, these numbers had reversed with 35% of participants with abnormal cough and 65% with present cough. The percentage of participants with a cough present at baseline level gradually increased over subsequent tests. At CRT6, 86% of the participants had recovered a reflexive cough to baseline level.

Summaries of the predictor variables are displayed in Tables 4 and 5. Analysis of data revealed that neither age, gender, length of intubation, endotracheal tube size, length of stay in ICU, discharge destination, cardiopulmonary bypass time, airway intubation grade, or Acute Physiology & Chronic Health Evaluation (APACHE) III score correlated with cough recovery.

The total morphine equivalent dose (mg/kg/hr) from initial morphine dose to completion of the study correlated significantly with time to return to baseline reflexive cough ($\chi^2(df)=17.0(3)$, $p=0.001$). Participants administered higher doses of opioids had a significantly shorter time to cough recovery. Analysis of morphine equivalent (mg/kg/hr) dose at CRT2 was completed to control for the confounding effect of time and tapering of dosing. A Mann-Whitney U test indicated that the distribution of opioid doses (mg/kg/hr) was the same in patients who had a cough present at CRT2 (Mdn=1.80) as in patients whose cough was abnormal at CRT2 (Mdn=1.17)($U=662$, $p=.239$).

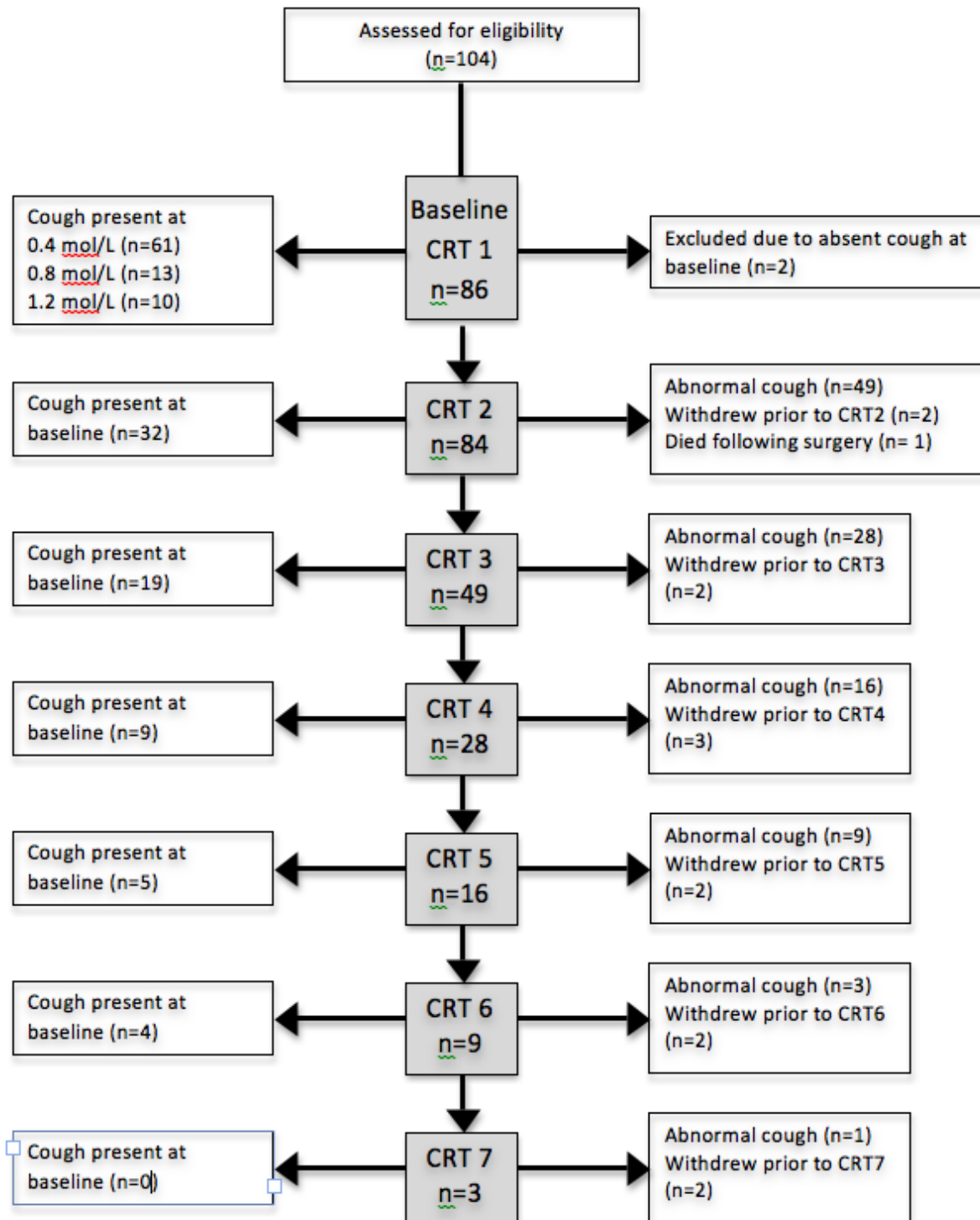


Figure 10. Flowchart outlining number of participants with a cough response present at baseline as well as presence or absence of baseline cough response and withdrawals at each follow-up point.

Table 3. Results of Each Follow-up CRT.

	Time post-extubation in hours	Proportion with cough at baseline (n^a)	Proportion with abnormal cough (n^b)
CRT2	M=1.16, SD=0.908	39.5% (n=32)	60.5% (n=49)
CRT3	M=12.0, SD=3.80	64.2% (n=53)	34.6% (n=28)
CRT4	M=24.5, SD=5.16	75.3% (n=61)	19.8% (n=16)
CRT5	M=38.1, SD=6.15	81.5% (n=66)	11.1% (n=9)
CRT6	M=48.4, SD=4.74	86.4% (n=70)	3.70% (n=3)
CRT7 ^c	69.4	98.8% (n=80)	1.23% (n=1)
CRT8	82.2	98.8% (n=80)	1.23% (n=1)
CRT9	93.7	98.8% (n=80)	1.23% (n=1)
CRT10	107	98.8% (n=80)	1.23% (n=1)
CRT11	117	98.8% (n=80)	1.23% (n=1)
CRT12	131	98.8% (n=80)	1.23% (n=1)

^a The number (n) of the total participants who had exhibited a baseline cough response by the follow-up.

^b The number (n) of the total participants who exhibited an abnormal cough response at the follow-up.

^c From CRT7, only one participant continued to be tested as all others had passed or withdrawn. Therefore, mean and standard deviation are not available.

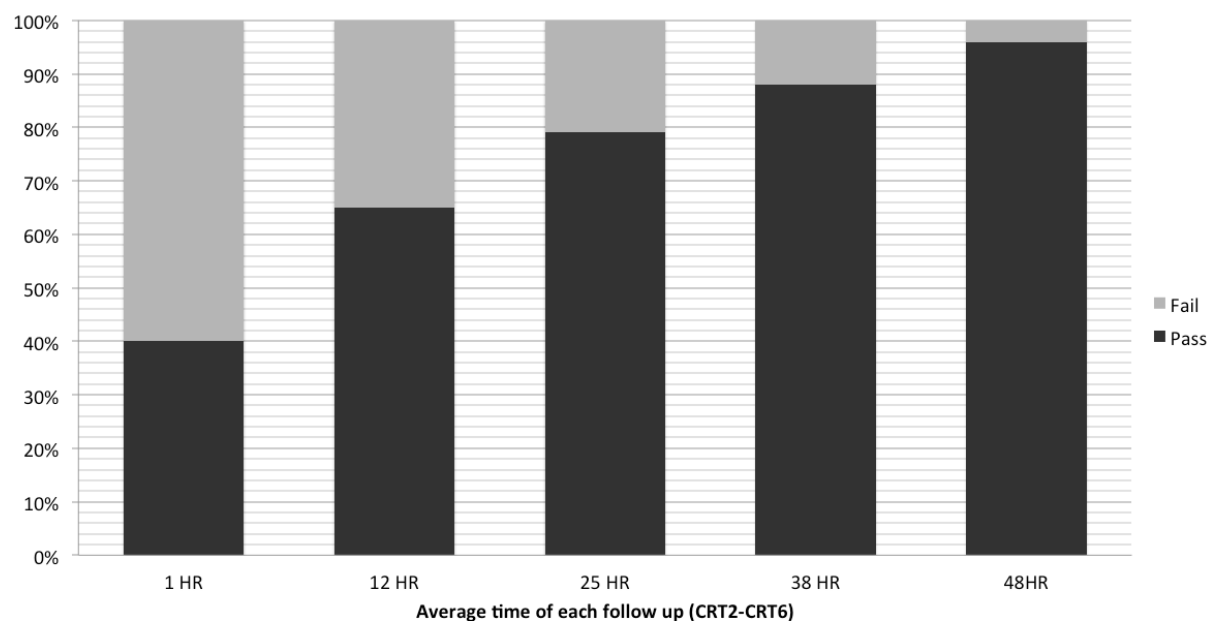


Figure 11. Results of CRT at each Follow-up CRT2 through CRT6.

Table 4. Summary of Continous Variables.

Continuous variables	Quartiles			$\chi^2(df)$	<i>p</i> value
	25th	50th	75th		
Age in years	60	66	70	0.93(3)	<i>p</i> =.818
Length of intubation in hours	8.75	10.2	13.3	3.73(3)	<i>p</i> =.293
Length of stay in ICU in hours	23	26	46	2.68(3)	<i>p</i> =.443
Length of bypass in minutes	74	93	111	1.95(3)	<i>p</i> =.584
APACHE III Score	34	38	45	0.955(3)	<i>p</i> =.812
Total morphine dose (mg/kg/hr)	0.088	0.175	1.14	17.0(3)	<i>p</i> =.001

Table 5. Summary of Categorical Variables.

Categorical Variables		<i>n</i>	χ^2 (df)	<i>p value</i>
Gender	Male	68	1.49(1)	<i>p</i> =.222
	Female	13		
Endotracheal tube size	7	3	3.91(5)	<i>p</i> =.562
	8	61		
	9	17		
Intubation Grade ^a	1	48	0.375(2)	<i>p</i> =.821
	2	27		
	3	3		
	Not recorded	3		
Discharge destination ^b	Home	65	2.35(2)	<i>p</i> =.309
	Other hospital	15		
	Died	1 ^c		

^a Cormack-Lehane Classification

^b Home, other hospital or died

^c Participant died as a result of a stroke after completing study participation

CHAPTER THREE

Study II

3 Study II: Comparison of CRT with VES in Recently Extubated ICU Patients

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is to determine the sensitivity and specificity of nebulized citric acid for detecting the presence of cough reflex on aspiration by analysing the relationship between response to CRT and presentation of airway compromise on endoscopy.

3.1.2 Secondary Objective

The secondary objective is to determine the prevalence of aspiration in this population, both overt and silent.

3.2 Material and Methods

3.2.1 Participants

Patients greater than 18 years of age who were admitted to ICU and required invasive ventilation were eligible for participation in this study. Patients who were receiving palliative care only were excluded. Because completion of the VES required ingestion of fluid, those who were strictly nil by mouth for surgical or gastrointestinal reasons or who were considered unsafe for oral intake due to a reduced Glasgow Coma Scale (GCS) score (patients scoring 12 or less) were also excluded. The study size was calculated to give 80% power to detect a reduction of sensitivity from 90% to 60% at the 0.05 level of significance (Li & Fine, 2004). Enrolment occurred between May and December 2014.

3.2.2 Procedures

Participants were enrolled after extubation. If a participant's GCS was less than 15, both the participant's assent and agreement of the next of kin was required for enrolment.

CRT and VES were performed within 24 hours of extubation by a single researcher. VES always followed CRT within one hour and was interpreted by a SLT blinded to CRT results. This ensured that the VES result could not influence CRT interpretation. In addition to performing CRT and VES, the researcher gathered demographic and treatment details, including admitting diagnosis, reason for intubation, length of intubation, APACHE III score, and morphine equivalent dose (mg/kg) in the 12 and 24 hours preceding testing. Where fentanyl was administered, the morphine equivalent dose was calculated assuming ten micrograms fentanyl was equivalent to one milligram morphine. The total morphine equivalent dose administered from time of induction to CRT was divided first by participant weight in kilograms then by the number of hours in this period to determine the administered mean morphine dose in milligrams per kilogram per hour (mg/kg/hr).

3.2.2.1 Cough Reflex Testing

Citric acid concentrations were selected based on previous research by Miles, Moore and colleagues (2013) that found 0.4 mol/L had optimal sensitivity and specificity for identifying silent aspiration when using a natural cough method. For this study, a suppressed cough method was used to guard against placebo cough and because it may represent a more accurate reflection of the true reflexive cough (Hegland et al., 2012). Also, the majority of patients admitted to the study ICU are intubated for cardiothoracic surgery and, as observed in Study I, these patients tend to suppress cough to avoid pain associated with coughing. Instructing all participants to suppress cough improved consistence of methods across participants. Normative data indicate that individuals' suppressed cough threshold is significantly higher than their natural cough threshold (Monroe et al., 2014), so concentrations of 0.4, 0.6 and 0.8 mol/L of 0.9% sodium chloride were selected. The citric acid solutions were prepared as per the recommendations of Falconer and colleagues (2014) in 5ml syringes by Optimus Healthcare Ltd. and were presented using a PulmoMate

Compressor/Nebulizer (Model 4650I, DeVilbiss Healthcare LLC, Pennsylvania, USA) with a predetermined free-flow output of 8 L/min and a restricted flow output of 6.6 L/min via a face mask.

Participants were seated upright to at least 60°. Supplemental oxygen was removed during delivery of aerosol, but returned between tests to avoid hypoxemia. The lowest concentration of citric acid, 0.4 mol/L, was presented first, followed by 0.6 and 0.8 mol/L until participants coughed. Citric acid was delivered for 15 seconds and participants were instructed to “breathe normally and try not to cough”. Each concentration was presented up to three times with a minimum of 1 minute between each presentation to prevent tachyphylaxis (Morice et al., 2007). In this study, cough is defined as a “forced expulsive maneuver or maneuvers against a closed glottis that are associated with a characteristic sound or sounds” as recommended in the ERS guidelines (Morice et al., 2007, p.1256). Nebulized 0.9% saline was randomly interspersed between citric acid doses (Morice et al., 2007). If a participant coughed on a trial of saline a second saline trial was administered. If the participant coughed on two trials of saline their cough was considered abnormal and they were excluded from the study. The cough reflex was considered present if the participant produced two or more audible successive coughs (C2) on two presentations of a single concentration. Cough reflex was classified as strong if the researcher judged the cough to be sufficient to clear aspirated material or weak if judged insufficient. If the participant produced a strong cough response at 0.4 or 0.6 mol/L the cough was assumed to be strong at higher concentrations. Increasing concentrations were presented until the cough reflex threshold was identified or judged absent.

3.2.2.2 VES

VES was performed at the participant’s bedside using an Olympus ENf-V2 Ultra Slim Rhino-laryngo-videoscope (Olympus Corporation, Shinjuku, Tokyo, Japan). Images were

recorded onto an Olympus IMH-10 image capture device. Participants did not receive topical anaesthesia. The scope was passed transnasally and the tip was positioned in the pharynx, allowing for a clear view of pharyngeal and laryngeal structures. Participants were asked to swallow five single sips of blue-dyed milk (or juice if unable to drink milk) via straw followed by approximately 150 millilitres via consecutive swallows. If they demonstrated aspiration on single sips they were not asked to take consecutive sips. The videos obtained from all studies were recorded on an external computer hard drive and later evaluated using the PAS (Rosenbek et al., 1996). Presence or absence of reflexive cough was also recorded.

3.3 *Statistical Analysis*

Statistical analyses were completed using SPSSv22 software (SPSS, Chicago, IL, USA). Generalized linear mixed effects analysis was completed to examine the data for relationships between the independent variables and both the presence and absence of cough reflex to CRT and the presence or absence of aspiration on VES. Descriptive statistics are presented as means with standard deviation or medians with interquartile range depending on the data distribution. Categorical data are presented as raw numbers and percentage. In cases where data were missing, no assumptions were made about missing data. A Mann-Whitney U test was performed to compare the distributions of time from extubation to CRT result data across different conditions. Sensitivity and specificity tables were created using Chi-squared tests. Analyses were completed with weak responses grouped with strong, and again with weak grouped with absent. When calculating sensitivity and specificity, Pearson's Coefficient was not appropriate because all tests had at least one group with an expected count of less than 10. Therefore, Fishers Exact Test was performed to determine significance. A priori significance level is set at $p < 0.05$ for all analyses.

3.4 *Results*

Recruitment began in May 2014 and was completed in December 2014. During that period, a total of 501 patients met eligibility criteria of which 112 (78 male) consented to participation. Five participants were excluded because they could not participate due to agitation or reduced GCS and one participant declined VES. Therefore, 106 participants underwent both CRT and VES. Participant characteristics are displayed in Table 6 and 7. Testing was initiated at a median of 17.7 hours post-extubation (IQR=9,22). Median intubation time was 12.4 hours (IQR=8.83,25.0). Thirteen of the 106 participants were intubated for 48 hours or greater.

Table 6. Participants Baseline Characteristics.

Total Participants		n=106
Age		Mdn=64 years, IQR=54,74
Gender	Male	78 (74%)
	Female	28 (26%)
Ethnicity	European	81 (76%)
	Māori	16 (15%)
	Other	9 (8%)
Reason for Admission	Surgical	77 (73%)
	Non-surgical	29 (27%)
Diagnosis	Cardiothoracic	69 (65%)
	Neurological	15 (14%)
	Cardiac	5 (5%)
	Pneumonia	3 (3%)
	Other	14 (13%)
GCS	>15	85 (80%)

Table 7. Summary of Continuous Predictor Variables.

	Median	IQR
Length of Intubation (in hours)	12.4	8.83, 25.0
APACHE III	40.0	33.3,47.8
Opioids in previous 12 hours^a	6.0	3.00,16.0
Opioids in previous 24 hours^a	20.0	10.0,33.0

^a Morphine Equivalent Dose (mg/kg/hr)

3.4.1 *CRT results*

Fifty-four percent of participants (n=57) had an absent cough reflex to CRT at 0.4 mol/L, 46% (n=49) at 0.6 mol/L and 37% (n=39) at 0.8 mol/L nebulized citric acid. The presence or absence of a cough reflex did not significantly correlate with age, gender, length of intubation, ethnicity, diagnosis, reason for intubation, APACHE III score or morphine equivalent dose (mg/kg/hr) at any concentration as shown in Table 8. There was no significant difference in the distributions of time from extubation to CRT data between those with a cough reflex response and those without a response when analysed by concentration, with weak cough responses grouped with strong cough responses and weak cough responses grouped with absent cough responses as displayed in Table 9.

Table 8. Results of Generalised Linear Mixed Effect Model Testing for Relationships Between Fixed Effects and CRT Result.

	F	(df1, df2)	p value
Age	1.59	(1,618)	.212
Length of Intubation	0.000	(1,618)	.961
Ethnicity	0.270	(5,618)	.929
Gender	0.928	(1,618)	.336
Reason for Admission	0.182	(1,618)	.670
Diagnosis	0.744	(4,618)	.562
APACHE III	0.228	(1,618)	.633
Opioids in previous 12 hours^a	0.217	(1,618)	.641
Opioid in previous 24 hours^a	0.218	(1,618)	.370

^a Morphine equivalent dose (mg/kg/hr)

Table 9. Results of Mann-Whitney U Test Comparing Distribution Between Time from Extubation to CRT and Results of CRT.

		U value	p value
0.4 mol/L	Weak responses grouped with strong (n=49)	1392	.854
	Weak responses group with absent (n=64)	1286	.614
0.6mol/L	Weak responses grouped with strong (n=57)	1366	.713
	Weak responses group with absent (n=58)	1292	.435
0.8 mol/L	Weak responses grouped with strong (n=68)	1251	.625
	Weak responses group with absent (n=48)	1251	.288

3.4.2 VES Results

Forty-five (42%) participants penetrated (PAS 2-5) and 13 (12%) aspirated (PAS 6-8) on VES. Of the participants who aspirated on VES, 9 (69%) did not cough in response to aspiration (PAS 8). Neither age, gender, ethnicity, diagnosis, reason for intubation, APACHE III score nor morphine equivalent dose (mg/kg/hr) were significant predictors of aspiration as displayed in Table 10. Intubation time was a significant predictor of aspiration ($\beta=-0.017$, $p<.01$). Figure 12 displays a boxplot of the intubation times for participants who did not aspirate (PAS 1-5) compared to participants who did aspirate (PAS 6-8). A Mann-Whitney U test determined that there was not a significant difference between the distributions of length of intubation between participants who silently aspirated ($n=3$) and participants who overtly aspirated ($n=10$) on VES ($U=882$, $p=.591$).

Table 10. Results of Generalised Linear Mixed Effects Model Testing for Relationships Between Fixed Effects and Presence of Aspiration on VES.

	<i>Aspiration</i>		
	F	(df1,df2)	p value
Age	0.006	(1,192)	.938
Length of Intubation	6.36	(1,192)	.013
Ethnicity	0.479	(5,192)	.791
Gender	0.115	(1,192)	.735
Reason for Admission	1.78	(1,192)	.184
Diagnosis	1.08	(4,192)	.366
APACHE III	0.711	(1,192)	.400
Opioids in previous 12 hours^a	3.40	(1,192)	.238
Opioids in previous 24 hours^a	0.218	(1,618)	.067

^a Morphine Equivalent Dose (mg/kg/hr)

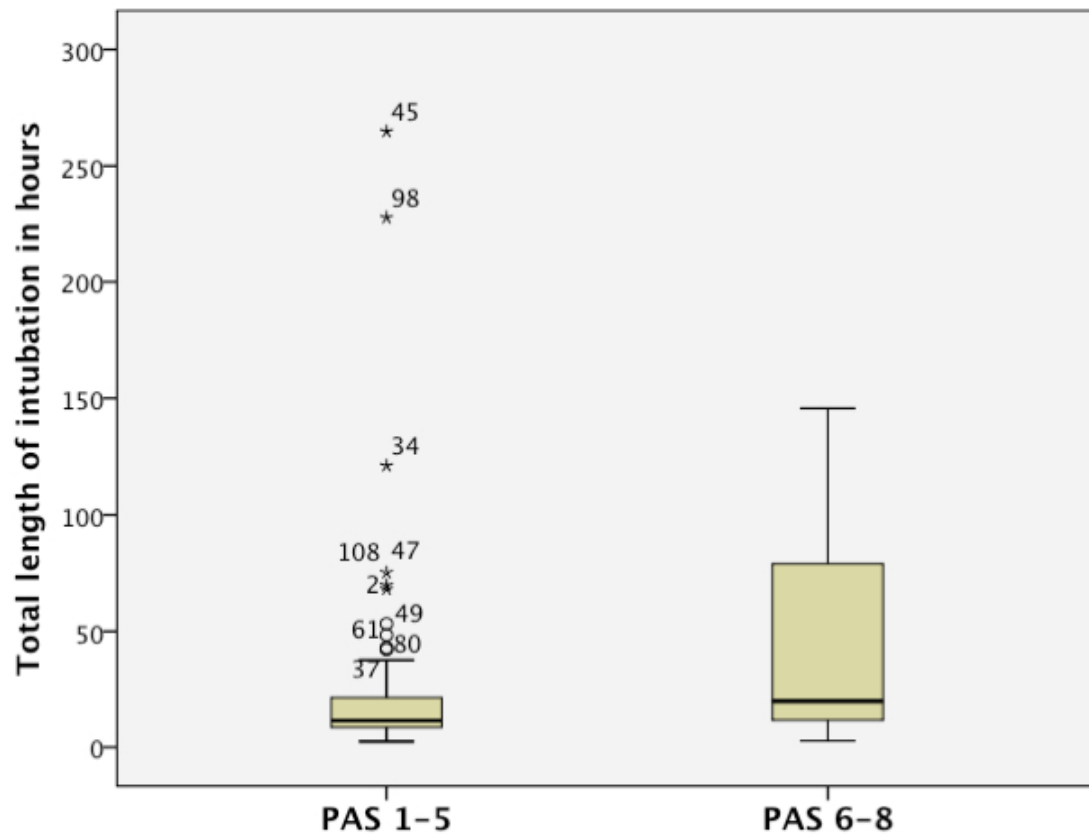


Figure 12. Boxplot of Intubation Duration by Absence (PAS 1-5) or Presence (PAS 6-8) of Aspiration on VES.

3.4.3 Sensitivity and Specificity

Sensitivity and specificity of CRT to predict silent aspiration on VES are displayed in Table 12. There was a significant relationship between CRT responses and the presence or absence of silent aspiration at all concentrations when weak responses were grouped with absent responses. Sensitivity of CRT to identify silent aspiration reached 100% in two conditions, at the concentrations of 0.4 and 0.6 mol/L, with weak cough responses grouped with absent responses. However, in both conditions, specificity was less than 50%.

Sensitivity and specificity of CRT to detect silent aspiration were optimized at 88% and 58% respectively at 0.8 mol/L citric acid with weak cough responses grouped with absent responses. The highest specificity for the whole cohort was achieved at 0.8 mol/L citric acid

when weak cough responses were grouped with strong (66%), but sensitivity in this condition was only 63%.

Table 13 displays the sensitivity and specificity values of CRT to detect aspiration on VES, which was optimized at optimized at 85% and 50% respectively at 0.6 mol/L citric acid with weak responses grouped with absent responses. There was a significant relationship between CRT responses and the presence or absence of aspiration at 0.4 and 0.6 mol/L when weak responses were grouped with absent responses. Table 14 displays the CRT results of participants grouped by PAS classification.

Table 11. Sensitivity, Specificity and Odds Ratio of CRT at Three Concentrations for Predicting Silent Aspiration on VES.

	Weak grouped with strong					Weak grouped with absent				
	Sensitivity	Specificity	<i>p</i> value ^a	Odds Ratio	95% CI	Sensitivity	Specificity	<i>p</i> value ^a	Odds Ratio	95% CI
0.4	75%	47%	.285	2.71	0.520,14.1	100%	42%	.021	N/A	N/A
0.6	75%	56%	.142	3.77	0.724, 19.6	100%	49%	.008	N/A	N/A
0.8	63%	66%	.135	323	0.727,14.4	88% ^b	58%	.022	9.56	1.13,80.8

^a Significance calculated using Fishers Exact Test

^b Optimal sensitivity and specificity

Table 12. Sensitivity, Specificity and Odds Ratio of CRT at Three Concentrations for Predicting Aspiraiton on VES.

Weak grouped with strong						Weak grouped with absent				
	Sensitivity	Specificity	<i>p</i> value ^a	Odds Ratio	95% CI	Sensitivity	Specificity	<i>p</i> value ^a	Odds Ratio	95% CI
0.4	77%	50%	.084	3.26	0.843,12.6	92%	44%	.014	9.46	1.18,75.8
0.6	69%	57%	.135	2.98	0.856,10.4	85% ^b	50%	.034	5.38	1.32,25.6
0.8	46%	57%	.538	1.63	0.506,5.27	62%	57%	.244	2.12	0.645,6.97

^a Significance calculated using Fishers Exact Test

^b Optimal sensitivity and specificity

Table 13. Breakdown of CRT Response by PAS Score. Data are Presented as Raw Number and (Percentage).

VES Result		PAS 1 (n=48)			PAS 2-5 (n=45)			PAS 6-8 (n=13)		
CRT Response		Absent	Weak	Strong	Absent	Weak	Strong	Absent	Weak	Strong
Concentration(mol/L)	0.4	22 (47%)	2	24	25	3	17	10	2	1
			(4%)	(51%)	(56%)	(7%)	(38%)	(77%)	(15%)	(8%)
	0.6	20 (43%)	2	26	20	5	20	9	2	2
			(4%)	(55%)	(44%)	(11%)	(44%)	(69%)	(15%)	(15%)
	0.8	16 (34%)	3	29	16	5	24	6	2	5
			(6%)	(62%)	(36%)	(11%)	(53%)	(46%)	(15%)	(38%)

3.4.4 *Prolonged intubation*

Thirteen participants were intubated for 48 hour or more. Five of the 13 (38%) participants aspirated (PAS 6-8) on VES, 3 (60%) without cough (PAS 8). Of the 79 (75%) participants who were intubated for less than 24 hours, 8 (8%) aspirated (PAS 6-8), 3 (38%) without a cough response (PAS 8). The sample size of participants with prolonged intubation was too small to calculate sensitivity and specificity in this cohort, but those participants' length of intubation, response to CRT and PAS score are provided in Table 14.

Table 14. Outcomes of Participants (n=13) who were Intubated for more than 48 Hours.

Participant	Length of Intubation	Cough at any concentration ^a	PAS	
1	53.3	Yes	1	
2	75.3	Yes	1	
3	68.2	Yes	2	Penetration ^b
4	69.8	Yes	3	
5	121	No	3	
6	48.4	Yes	3	
7	265	No	4	
8	228	No	5	
9	79.0	Yes	7	Aspiration ^b
10	95.2	No	7	
11	91.3	No	7	
12	72.3	Yes	8	Silent
13	145	Yes	8	Aspiration ^b

^a Did the patient cough to any concentration of citric acid?

^b According to Rosenbek et al., 1996

3.4.5 *Neurological Patients*

The characteristics of the 14 participants with a neurological diagnosis are listed in Table 15. Participants with a neurological diagnosis had a lower median age (Mdn = 59.0, IQR = 46.0, 72.0) than participants with other diagnoses (Mdn = 65.0, IQR = 55.0, 74.0). Participants with a neurological diagnosis also had a longer median intubation time (Mdn = 20.4, IQR = 8.64, 53.4) than their non-neurological participants (Mdn = 11.8, IQR = 8.75, 21.8). Twenty-five percent of participants with a neurological diagnosis had an absent cough reflex at all concentrations of citric acid compared to 64.3% of participants with a non-neurological diagnosis. Two of the 14 participants aspirated on VES, one of these without a cough response. The participant who silently aspirated had a weak cough response on 0.4, 0.6 and 0.8 mol/L citric acid. The sample size of participants with a primary neurological diagnosis was too small to calculate sensitivity and specificity in this cohort, but those participants' length of intubation, response to CRT and PAS score are provided in Table 15. Only two of the participants with a neurological diagnosis had an absent cough and both of these participants penetrated above the vocal cords (PAS 3).

Table 15. Characteristics of Participants Admitted with a Primary Neurological Diagnosis

Age	Length of intubation ^a	APACHEIII	CRT Result ^b	PAS Score	
72	21.5	37	Yes	1	
49	19.7	38	Yes	1	
75	21.0	50	Yes	1	
47	17.6	31	Yes	1	
31	2.58	29	Yes	1	
62	68.2	32	Yes	2	
72	9.83	52	No	3	
54	2.50	42	Yes	3	
63	48.4	35	Yes	3	Penetration ^c
19	121	26	Yes	3	
56	5.08	35	Yes	3	
43	37.7	24	No	3	
62	19.5	37	Yes	6	Aspiration ^c
77	72.3	42	Yes	8	Silent Aspiration ^c

^a Total length of intubation in hours

^b Did the patient cough to any concentration of citric acid?

^c According to Rosenbek et al., 1996

PART C: DISCUSSION

CHAPTER FOUR

Discussion, Limitations & Future Research

4 Discussion, Limitations and Future Research

This thesis describes the first research programme to systematically evaluate the cough reflex in post-extubated ICU patients and validate CRT for identifying silent aspiration in this population. In summary, in Study I, cough reflex was frequently impaired following extubation. In addition, impaired cough reflex often persisted for up to 48 hours following extubation in patients undergoing CABG. More than a quarter of participants in Study II aspirated on VES within 24 hours of extubation. However, diagnostic specificity of CRT was poor, despite significant relationships between response to CRT and aspiration.

There is significant clinical value in improving the assessment of swallowing in ICU and, particularly, in identifying patients at risk of silent aspiration. There is evidence that ICU patients with impaired airway reflexes are more likely to develop pneumonia (Chevret et al., 1993). Patients who develop pneumonia stay in hospital longer, cost more to treat and are more likely to die (Safdar et al., 2005). The results of Studies I and II indicate that ICU patients are at high risk of impaired cough reflex following extubation, especially within the first few hours. Given the reported links between absent cough reflex and pneumonia (Addington, Stephens, & Gilliland, 1999; Davies, 2016), it seems likely that patients with impaired cough reflex after extubation would be at a greater risk of developing pneumonia than their counterparts with intact cough reflex.

Any pneumonia that occurs within 24 hours of extubation is labelled as VAP. Although the precise contribution of impaired cough reflex to VAP has not been investigated, impaired airway reflexes at the time of intubation has been identified as a predictor of VAP (Chevret et al., 1993). In addition, aspiration of oral or gastric contents is considered to be a major contributor to VAP (Bouza et al., 2003; Bouza et al., 2008; Safdar et al., 2005). Participant age, APACHE score, and length of intubation have previously been linked to the development of VAP in ICU (Apostolopoulou, Bakakos, Katostaras, & Gregorakos, 2003;

Lewis, Li, Murphy, & Klompas, 2014; Weinstein, Bonten, Kollef, & Hall, 2004). Interestingly, none of these variables correlated with the presence or absence of cough reflex in the current research programme. However, because patient outcomes were not gathered in this study, including the development of pneumonia, limited conclusions can be drawn about the relationship between CRT and VAP in the ICU population.

4.1 *Impact of Intubation on Cough Reflex*

Intubation appears to have a statistically and clinically significant impact on the cough reflex, which is most marked in the few hours immediately following extubation, but can persist for two days or longer. Interestingly, impaired cough appears to occur as frequently after short periods of intubation as after prolonged intubation. This is consistent with the findings of Tanaka and colleagues (2005) who reported that the cough reflex was impaired in 100% of study participants following brief intubation for minor surgery. There is ample evidence in the research that orotracheal intubation causes trauma to the larynx after even short periods of intubation (Heffner, 2010) and this seems the most plausible cause for impaired cough. Although not systematically evaluated, anecdotally many participants in Study II had evidence of laryngeal trauma on VES. Colton House and colleagues (2011) suggested that dysphagia could occur as a result of injury to the laryngeal tissues causing oedema, ulceration and granulation of the tissue or damage to the RLN as a result cuff pressure (Colton House et al., 2011). It seems plausible that these factors could also contribute to impaired cough reflex. True cough receptors are concentrated in the larynx and trachea and damage to these tissues may affect the sensitivity of these receptors. In addition, the RLN is essential for swallowing (Canning et al., 2004) and damage to the nerve from cuff pressure would likely impact cough.

Other proposed causes of post-extubation dysphagia, including weakness from muscle atrophy (Brown et al., 2011; DeVita & Spierer-Rundback, 1990; Tolep et al., 1996) and

disruption in respiration (de Camargo, Ono, Park, Caruso & Carvalho, 2010), seem less likely to contribute to cough reflex impairment. Although muscle weakness would likely lead to weak cough, it would not explain absent cough. Similarly, disruption in respiration may contribute to abnormal or weak cough, but not absent cough. The designs of Studies I and II were not sufficient to determine the cause of cough impairment, but this remains an important area of research. Further research evaluating the relationship between presence, location and severity of laryngeal injury and cough reflex impairment would be particularly beneficial.

4.2 *Aspiration Following Extubation*

Aspiration prevalence has been reported to range from 22% to 56% in studies where all patients underwent instrumental assessment regardless of the presence or absence of signs or symptoms of dysphagia (Ajemian et al., 2001; El Solh et al., 2003; Leder et al., 1998; Scheel et al., 2016). This range reflects varied patient groups in different ICU settings and varied enrolment criteria. The prevalence of aspiration amongst our cohort was below this range at 12%. The most likely explanation for this variance is that previous studies all enrolled participants following 48 hours or more of intubation, while Study II included participants following intubation periods of any length. In fact, the median length of intubation in Study II was just 12 hours. There were only 13 participants in Study II who were intubated for 48 hours or longer and five (38%) of these participants aspirated ($PAS \geq 6$). An aspiration rate of 38% in participants who have been intubated for 48 hours or more is consistent with previous studies. Similarly, although only 9 of 112 (8%) participants silently aspirated on VES, 2 out of 13 (15%) of the participants who were intubated more than 48 hours aspirated silently. Others have reported a prevalence of silent aspiration of 8% (Scheel et al., 2016) to 25% (Ajemian et al., 2001) amongst ICU patients who have been orotracheally intubated for more than 48 hours. Although the number of participants in Study II with prolonged intubation was too small for detailed analysis, the percentage of

participants who aspirated and silently aspirated in the current study appears to be in line with other studies.

Length of intubation was the only factor that correlated significantly with the presence of aspiration in Study II. This is in agreement with several other studies that reported a link between prolonged intubation and development of dysphagia (Barker et al., 2009; Bordon et al., 2011; Brown et al., 2011; Hogue et al., 1995; Kwok et al., 2013; Macht et al., 2011; Malandraki et al., 2016; Rousou et al., 2000). However, it is important to note that Study II measured aspiration specifically and not dysphagia, which may be present without aspiration. Previous studies evaluating post-extubation aspiration on instrumental assessment have not found a relationship between length of intubation and prevalence of aspiration (Ajemian et al., 2001; Barquist et al., 2001; El Solh et al., 2003; Leder et al., 1998; Scheel et al., 2016). This may be because these studies all excluded patients who had been intubated for less than 48 hours and, as reported in Study II, participants with shorter periods of intubation are less likely to aspirate. Therefore, Study II offers unique information about the relationship between intubation length and risk of aspiration.

Although patients with longer periods of intubation were more likely to aspirate, Study II is the first research to demonstrate that aspiration and silent aspiration occurred in participants who were intubated for only a short period. There are no previous studies in a general ICU setting in which all participants underwent instrumental assessment, regardless of presence or absence of overt symptoms of dysphagia or length of intubation. Studies that only include patients who have been intubated for more than 48 hours overlook the real and clinically significant problem of dysphagia after short periods of intubation.

There are a number of reasons that ICU patients would have dysphagia, and specifically aspiration, following extubation. As a group these patients display a number of risk factors. Seventy-three percent of participants in Study II were admitted to ICU following

a surgery. As identified in the literature review, patients undergoing surgery have an increased risk of dysphagia due to perioperative stroke (Selim, 2007), cranial nerve damage (DiLisio et al., 2013), supine positioning (Aderinto - Adike & Quigley, 2014) and altered sensorium (Schenning & Deiner, 2015).

Fourteen percent of patients in Study II had a primary neurological diagnosis. Given the high prevalence of dysphagia in patients with neurological disorders (Mackay et al., 1999; Mann et al., 2000), it may be presumed that some participants in Study II may have had dysphagia resulting from primary neurological impairment as well as a secondary impact of intubation. Interestingly, the prevalence of absent cough reflex was actually lower in the neurological group (14%) than the entire cohort (37%). Prevalence of aspiration was very similar between the two groups, at 14% in the neurological group compared to 12% in the total cohort, as was prevalence of aspiration, at 7% in the neurological group compared to 8% in the total cohort. However, with only two participants in the neurological group having absent cough to CRT and two aspirating on VES, one overtly and one silently, the numbers are simply too small to support or refute the theory of neurological injury impairing both swallowing and cough in this cohort.

Another potential cause of dysphagia and aspiration in the ICU population is the use of opioids. Many of the participants in both studies were prescribed opioids in the 24 hours preceding CRT assessment. Although the opioid dose did not correlate with aspiration in Study II, opioids are known to result in an impaired level of consciousness in patients (Devlin, 2009), which may put them at increased risk of dysphagia. The above risk factors combine in any individual patient to create a complex picture of risk and for this reason, it is impossible to determine the specific cause of dysphagia after extubation.

4.3 *Impact of Opioids*

The issue of opioids requires additional discussion. Patients routinely receive opioids during mechanical ventilation and in the hours following extubation for sedation and analgesia (Elliott et al., 2013). Kelly and colleagues (2016) examined the effect of fentanyl on cough and reported that clinically relevant doses of fentanyl diminish the cough reflex. They reported an average time of 45 minutes from cessation of fentanyl administration to a participant's return to baseline cough sensitivity. In addition to the carefully controlled doses of opioids delivered in theatre and during unconscious sedation, all patients in Study I and many in Study II were able to self-administer opioids via a patient-controlled analgesia system. In addition, opioids can affect men differently than women (Lee & Ho, 2013). As a result, the total effective opioid dose varied widely from patient to patient. These factors make it very difficult to control precisely for opioid dose when performing research in the ICU setting.

In Study I, there was a highly significant relationship between morphine equivalent dose and time to return of a participant's baseline cough sensitivity, with those patients who received larger doses of opioids returning more quickly to their baseline cough reflex threshold. This is counterintuitive given the anti-tussive properties of opioids and is most likely a result of dosing patterns rather than a cause and effect relationship between increasing opioid dose and greater cough reflex sensitivity. The pattern of opioid administration was peak dosing in the intra-operative period with gradual tapering of dosing over the hours and days following extubation as a participant's pain subsided. Therefore, participants who recovered their cough reflex sooner were more likely to have a higher per hour mean opioid dose.

In Study II, when CRT was performed only once within 24 hours of extubation, there was no relationship between opioid dose and the presence or absence of cough as might have

been expected. Any effect that opioids had on cough reflex may have been masked by the more substantial effect of intubation. Although no firm conclusions can be drawn from these studies regarding the effects of opioids on the cough reflex and swallowing, the presence of cough in many participants immediately following extubation, shortly after the period of peak dosing, suggests that opioid use was not the primary factor in impairment of cough reflex in these participants.

4.4 *Validity of CRT after Extubation*

CRT achieved high sensitivity for identifying patients who silently aspirate post-extubation in Study II, but specificity was consistently poor. CRT correctly identified most or, in the case of 100% sensitivity, all participants who silently aspirated on VES. However, it also identified many participants as silent aspirators when they did not silently aspirate on VES. Use of CRT in this population would grossly over-identify silent aspiration risk. For example, based on these data, only 13 of every 100 patients with an absent or weak cough to CRT at 0.4 mol/L would silently aspirate, 14 at 0.6 mol/L and 15 at 0.8 mol/L. A strict CRT protocol as has been proposed for stroke patients (Davies, 2016), in which patients with an absent cough would be kept nil by mouth until instrumental assessment, would create unnecessary discomfort to patients, risk of malnutrition and missed medications and increased costs to the health system for limited clinical gain.

These results contrast with the findings of previous studies in different patient populations, which report specificity figures as high as 0.89 (Miles, Moore, et al., 2013; Wakasugi et al., 2008). One explanation for the difference may be that both Miles, Moore and colleagues (2013) and Wakasugi and colleagues (2008) recruited only participants who presented with symptoms of dysphagia while Study II included all patients regardless of the presence or absence of overt signs of dysphagia. The wider inclusion criterion is a strength of this study and increases its external validity.

CRT is a test of cough sensitivity. Specifically, it measures the body's ability to detect and respond to irritant stimuli. The cough reflex is an important component of airway protection during swallowing, but individuals can have an absent cough reflex and not be dysphagic. This would especially be the case if the mechanism causing dysphagia were different than the mechanism causing impairment of the cough reflex. If the causes were the same, one could expect validity of CRT to predict silent aspiration. However, if swallowing impairment were independent of cough impairment, which these results suggest, individuals with an absent cough reflex may not be dysphagic. This would result in low specificity as reported in Study II.

The higher specificity figures reported by Wakasugi and colleagues (2008) and Miles, Moore and colleagues (2013) when compared to Study II support the argument that the causes of post-extubation dysphagia and impaired cough reflex are different. Fourteen percent of participants in Study II had a primary neurological diagnosis compared to 59% (Miles, Moore, et al., 2013) and 56% (Wakasugi et al., 2008). Given altered neurology can affect both swallowing and the cough reflex, specificity of CRT may be higher in patient groups with a high prevalence of neurological disorders. In patients without a neurological impairment, the mechanism of cough impairment may be more likely to be independent of swallowing impairment. In Study II, only two of the 14 participants with a neurological diagnosis aspirated on VES, on silently, and both of these participants had a cough response to CRT. Two different participants had an absent cough to CRT and both penetrated to a level above the vocal cords and did not eject the material. The sample size of Study II is too small to draw specific conclusions on the link between aspiration and CRT in this cohort.

It is interesting to note that sensitivity of CRT to predict aspiration and silent aspiration was consistently higher when weak cough responses were grouped with absent responses, indicating that participants with a weak cough were more likely to aspirate. This is

consistent with the findings of Miles, Moore and colleagues (2013). Patients who are weak as a symptom of their illness or a sequelae of their treatment may be more likely to experience concurrent dysphagia, contributing to greater sensitivity.

4.5 *Clinical Implications*

Currently there are no standardised assessment protocols for the ICU post-extubation population and no standardly accepted criteria for resuming oral intake following extubation. In the hospital where these studies were conducted, patients are routinely allowed water as soon as 30 minutes after extubation. If patients have an obvious neurological deficit or cough persistently with oral intake they may be referred at the discretion of the patient's nurse or doctor to the SLT for swallowing assessment. However, a patient with an absent cough reflex may aspirate without overt signs, making it unlikely to detect at bedside by even the most observant nurse and consequent referral to SLT unlikely.

This research supports several other studies in finding that post-extubation dysphagia can occur and patients are at increased risk of aspiration, both overt and silent, in the 24 hours following extubation. In addition, both studies identify that many participants had an impaired cough reflex following intubation. The cough reflex is one of the key airway defence mechanisms (Pitts et al., 2013). Clinical assessment is based on the observation of overt signs of aspiration, including coughing, and does not identify silent aspiration. Although CRT had poor specificity as a screening tool for silent aspiration, it may still have a place as one of the clinician's tools for assessment. When used with patients who are at the highest risk of dysphagia, including those with primary neurological diagnoses and those who have been intubated for extended periods of time, CRT may still provide useful information about integrity of sensation and the need for instrumental assessment. On-going research that contributes to the development of validated and standardised assessment of dysphagia in the post-extubation would be welcome.

4.6 *Limitations of the Studies*

There are several limitations to this research programme. Eleven participants withdrew from Study I, citing discomfort caused by coughing. Encouraging coughing following CABG is routine practice, despite the discomfort it causes, and patients all had access to analgesia to decrease pain associated with coughing. The researcher noted that participants were more likely to withdraw as the study progressed. It is impossible to know at what point these participants would have returned to baseline CRT sensitivity, but the withdrawal of participants likely biased the results. This bias cannot be overcome in any study in which participants have the freedom to withdraw.

Another limitation is the length of time between testing points. In Study I, there was an average of 12 hours between each follow-up point. A participant may have had an absent cough reflex at 12 hours following extubation. His cough reflex may have returned at 13 hours, but not have been measured and recorded as present until the next follow-up at 24 hours following extubation. Because of this, average time to baseline cough recovery could not be reported. Ideally, CRT would have been repeated more frequently, perhaps every three hours. However, this is unrealistic as there likely would have been a much higher rate of participant withdrawal.

In study two, the range of citric acid concentrations was a limitation of this study and if we had included a wider range, including citric acid concentrations below 0.6 mol/L, specificity may have improved. Indeed, Miles, Moore and colleagues (2013) reported improved specificity with decreasing concentrations of citric acid. However, many patients in ICU fatigue easily and have a limited ability to attend to a task and the CRT and VES needed to be performed within one hour. Thus, it was not practical to perform a lengthy assessment and CRT trials were kept to a minimum.

Analysis of opioid effect on cough recovery was limited and confounded by the effect of tapering doses. Patient variability in opioid clearance and sensitivity along with differing opioid types and doses administered meant that measuring a true opioid effect in this population was difficult and beyond the scope of this study.

Finally, participant outcomes were not included as part of this study. Although many patients had an impaired cough reflex or aspiration following extubation, we do not know if those participants had poorer outcomes than their peers without impairment of cough or swallowing. Previous research indicates that patients with dysphagia have poorer outcomes (Safdar et al., 2005), but there has been no research on the impact of an impaired cough reflex in the absence of dysphagia.

4.7 *Future Research*

These studies provide valuable insights into the effect of intubation on the cough reflex, aspiration and the link between the two, but there is much we don't know. Researchers have previously reported that CRT has reasonable sensitivity and specificity for predicting which patients are at the greatest risk of silent aspiration (Miles, Moore, et al., 2013; Wakasugi et al., 2008). The poor specificity reported in Study II suggests that validity of CRT for predicting silent aspiration varies in different patient populations. Clearly, more research is needed to clarify in which patient populations CRT is most useful. Future research with larger sample sizes of ICU participants that include a wider range of pathologies would allow for analysis of subgroups to determine if post-extubation CRT validity differs by diagnosis. Ideally, studies should include participants both with and without clinical signs of dysphagia.

Considering the specificity of CRT to predict silent aspiration was poor, the mechanism of impairment of cough reflex and silent aspiration is presumably different in at least some cases. In other patient groups, including those who have had a stroke, a single

event may impair both swallowing and the cough reflex. It seems likely that cough can be impaired by neurological insult, such as damage to the brainstem or cortical pathways of cough, as well as by localized laryngeal trauma. Further research could tease out these different types of cough impairment and their relevance to swallowing assessment.

This study does indicate that aspiration, both overt and silent, and impaired cough reflex occur after short periods of intubation. The median length of intubation in study II was twelve hours and many participants with relatively short periods of intubation had impaired cough. The majority of research studies to date have included only participants who were intubated for greater than 48 hours (Ajemian et al., 2001; Barker et al., 2009; Barquist et al., 2001; Bordon et al., 2011; Daly et al., 2016; El Solh et al., 2003; Leder et al., 1998; Noordally et al., 2011; Padovani et al., 2008; Scheel et al., 2016), although it is not clear where this delineation originated. Future studies should include participants with widely varying durations of intubation. In addition to the ICU population, it would be worthwhile assessing the cough reflex with CRT in patients with even shorter periods of intubation who are not admitted to ICU. Research by Tanaka and colleagues (2005) suggests that patients do not cough to water injected into the glottis following brief intubation. There is still much to be learned about the effect of intubation on cough.

Another point that requires further exploration is the mechanism of post-extubation cough impairment. There is a range of theories for how intubation affects swallowing, including laryngotracheal trauma, muscle atrophy (Brown et al., 2011) and disruption of respiration (de Camargo et al., 2010). There is less written about the possible causes of the attenuation of the cough reflex post-extubation, but possibilities include neurological adaptation (Hasegawa & Nishino, 1999; Tanaka et al., 2005) and the administration of opioids (Chung & Chang, 2002) and laryngeal injury. Laryngeal injury is common following extubation (Colton House et al., 2011; Scheel et al., 2016; Tadie et al., 2010), although the

relationship between laryngeal injury and cough reflex has not been studied. Future research into the cough reflex following intubation should include observation, classification and grading of laryngeal injury.

Opioids are known to impair the cough reflex, although there was not a significant relationship between opioid dose and cough reflex sensitivity in Study II. To examine the role of opioids, it would be ideal to study patients who were intubated but did not receive opioids. Unfortunately, this isn't practical in a clinical setting as sedation for intubation usually includes opioids. At a minimum, studies looking at cough recovery should record opioid dose and attempt to control for the effect of opioids when analysing results of CRT.

Finally, the significance of impaired cough reflex in the absence of aspiration warrants further research. There is evidence that absent cough in the stroke population is associated with a greater risk of pneumonia (Addington, Stephens, & Gilliland, 1999; Davies, 2016), but this has not been investigated in the ICU population. The results of Studies I and II indicate that many patients have an absent cough in the 48 hours following intubation, but the clinical significance of this is unknown.

4.8 *Conclusions*

This is the first systematic programme of study to evaluate the cough reflex following extubation in the ICU population and to look at the recovery of cough reflex. It is also the first attempt to determine the validity of CRT in this population. The results confirm that the cough reflex is impaired following orotracheal extubation, but usually returns to baseline within 48 hours of extubation. In addition, aspiration, both overt and silent, often occurs in the 24 hours following extubation. Both can occur after even short periods of intubation, though patients who are intubated for longer periods are more likely to aspirate. Because cough is often impaired following extubation, clinical assessment may not be reliable. However, CRT is not a valid tool to use to identify patients who are likely to silently aspirate.

REFERNECES

- Addington, W. R., & Stephens, R. E. (1999). United States of America Patent No. 6,004,268.
U. S. Patent Office: <https://www.google.com/patents/US6004268>
- Addington, W. R., Stephens, R. E., Gilliland, K., & Miller, S. P. (1998). Tartaric acid-induced cough and the superior laryngeal nerve evoked potential. *Am J Phys Med Rehabil*, 77(6), 523-526.
- Addington, W. R., Stephens, R. E., Gilliland, K., & Rodriguez, M. (1999). Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke. *Arch Phys Med Rehabil*, 80(2), 150-154.
- Addington, W. R., Stephens, R. E., & Gilliland, K. A. (1999). Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke: an interhospital comparison. *Stroke*, 30(6), 1203-1207.
- Addington, W. R., Stephens, R. E., & Goulding, R. E. (1999). Anesthesia for the superior laryngeal nerves and tartaric acid-induced cough. *Arch Phys Med Rehabil*, 80(12), 1584-1586.
- Addington, W. R., Stephens, R. E., Ockey, R., Kann, D., & Rodriguez, M. (1995). A New Aspiration Screening Test to Assess the Need for Modified Barium Swallow Study - Addington. *Arch Phys Med Rehabil*, 76, 1040.
- Addington, W. R., Stephens, R. E., Widdicombe, J. G., & Rekab, K. (2005). Effect of stroke location on the laryngeal cough reflex and pneumonia risk. *Cough*, 1, 4.
doi:10.1186/1745-9974-1-4
- Aderinto - Adike, A. O., & Quigley, E. M. (2014). Gastrointestinal motility problems in critical care: a clinical perspective. *Journal of digestive diseases*, 15(7), 335-344.

- Ajemian, M. S., Nirmul, G. B., Anderson, M. T., Zirlen, D. M., & Kwasnik, E. M. (2001). Routine fiberoptic endoscopic evaluation of swallowing following prolonged intubation: implications for management. *Arch Surg*, 136(4), 434-437.
- Amri, M., & Car, A. (1988). Projections from the medullary swallowing center to the hypoglossal motor nucleus: A neuroanatomical and electrophysiological study in sheep. *Brain Res*, 441(1-2), 119-126.
- Ando, A., Farrell, M. J., & Mazzone, S. B. (2014). Cough-related neural processing in the brain: a roadmap for cough dysfunction? *Neuroscience & Biobehavioral Reviews*, 47, 457-468.
- Apostolakis, E., Papakonstantinou, N. A., Baikoussis, N. G., & Papadopoulos, G. (2015). Intensive care unit-related generalized neuromuscular weakness due to critical illness polyneuropathy/myopathy in critically ill patients. *Journal of anesthesia*, 29(1), 112-121.
- Apostolopoulou, E., Bakakos, P., Katostaras, T., & Gregorakos, L. (2003). Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. *REspiratory Care*, 48(7), 681-688.
- Armstrong, W. B., & Netterville, J. L. (1995). Anatomy of the larynx, trachea, and bronch. *Otolaryngol Clin North Am*, 28(4), 685.
- Aviv, J. E. (2000). Prospective, randomized outcome study of endoscopy versus modified barium swallow in patients with dysphagia. *Laryngoscope*, 110(4), 563-574.
- Aviv, J. E., Kim, T., Sacco, R. L., Kaplan, S., Goodhart, K., Diamond, B., & Close, L. G. (1998). FEESST: a new bedside endoscopic test of the motor and sensory components of swallowing. *Ann Otol Rhinol Laryngol*, 107(5 Pt 1), 378-387.
- Badr, C., Elkins, M. R., & Ellis, E. R. (2002). The effect of body position on maximal expiratory pressure and flow. *Australian Journal of Physiotherapy*, 48(2), 95-102.

- Barker, J., Martino, R., Reichardt, B., Hickey, E. J., & Ralph-Edwards, A. (2009). Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. *Can J Surg*, 52(2), 119-124.
- Barquist, E., Brown, M., Cohn, S., Lundy, D., & Jackowski, J. (2001). Postextubation fiberoptic endoscopic evaluation of swallowing after prolonged endotracheal intubation: A randomized, prospective trial. *Critical Care Medicine*, 29(9), 1710-1713.
- Barros, M. J., Zammattio, S. J., & Rees, P. J. (1990). Importance of inspiratory flow rate in the cough response to citric acid inhalation in normal subjects. *Clinical Science*, 78(5), 521-525.
- Bastian, R. W., & Riggs, L. C. (1999). Role of sensation in swallowing function. *Laryngoscope*, 109(12), 1974-1977.
- Baumgartner, C. A., Bewyer, E., & Bruner, D. (2008). Management of Communication and Swallowing in Intensive Care. *AACN Advanced Critical Care*, 19(4), 433-443.
- Becklake, M. R., & Kauffmann, F. (1999). Gender differences in airway behaviour over the human life span. *Thorax*, 54(12), 1119-1138.
- Bhattacharyya, N. (2014). The prevalence of dysphagia among adults in the United States. *Otolaryngology--Head and Neck Surgery*, 151(5), 765-769.
- Bickerman, H. A., & Barach, A. L. (1954). The experimental production of cough in human subjects induced by citric acid aerosols; preliminary studies on the evaluation of antitussive agents. *Am J Med Sci*, 228(2), 156-163.
- Bickerman, H. A., German, E., Cohen, B. M., & Itkin, S. E. (1957). The cough response of healthy human subjects stimulated by citric acid aerosol. II. Evaluation of antitussive agents. *Am J Med Sci*, 234(2), 191-206.

- Bishop, M. J., Hibbard, A. J., Fink, B. R., Vogel, A. M., & Weymuller, E. A., Jr. (1985). Laryngeal injury in a dog model of prolonged endotracheal intubation. *Anesthesiology*, 62(6), 770-773.
- Bordon, A., Bokhari, R., Sperry, J., Testa, D. t., Feinstein, A., & Ghaemmaghami, V. (2011). Swallowing dysfunction after prolonged intubation: analysis of risk factors in trauma patients. *Am J Surg*, 202(6), 679-682; discussion 682-673. doi:10.1016/j.amjsurg.2011.06.030
- Bouza, E., Pérez, A., Muñoz, P., Pérez, M. J., Rincón, C., Sánchez, C., . . . Riesgo, M. (2003). Ventilator-associated pneumonia after heart surgery: a prospective analysis and the value of surveillance. *Critical Care Medicine*, 31, 1964-1970.
- Bouza, E., Pérez, M. J., Munoz, P., Rincón, C., Barrio, J. M., & Hortal, J. (2008). Continuous aspiration of subglottic secretions in the prevention of ventilator-associated pneumonia in the postoperative period of major heart surgery. *Chest*, 135(5), 938-946.
- Brooks, S. M. (2011). Perspective on the human cough reflex. *Cough*, 7, 10. doi:10.1186/1745-9974-7-10
- Brown, C. V., Hejl, K., Mandaville, A. D., Chaney, P. E., Stevenson, G., & Smith, C. (2011). Swallowing dysfunction after mechanical ventilation in trauma patients. *J Crit Care*, 26(1), 108 e109-113. doi:10.1016/j.jcrc.2010.05.036
- Burgess, G. E., 3rd, Cooper, J. R., Jr., Marino, R. J., Peuler, M. J., & Warriner, R. A., 3rd. (1979). Laryngeal competence after tracheal extubation. *Anesthesiology*, 51(1), 73-77.
- Canning, B. J. (2006). Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. *Chest*, 129(1 Suppl), 33S-47S. doi:10.1378/chest.129.1_suppl.33S
- Canning, B. J., Mazzone, S. B., Meeker, S. N., Mori, N., Reynolds, S. M., & Undem, B. J. (2004). Identification of the tracheal and laryngeal afferent neurones mediating cough

- in anaesthetized guinea-pigs. *J Physiol*, 557(Pt 2), 543-558.
doi:10.1113/jphysiol.2003.057885
- Canning, B. J., & Mori, N. (2011). Encoding of the cough reflex in anesthetized guinea pigs. *Am J Physiol Regul Integr Comp Physiol*, 300(2), R369-377.
doi:10.1152/ajpregu.00044.2010
- Carnaby-Mann, G., & Lenius, K. (2008). The bedside examination in dysphagia. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 747-768.
- Chang, A. B., & Widdicombe, J. G. (2007). Cough throughout life: children, adults and the senile. *Pulm Pharmacol Ther*, 20(4), 371-382.
- Chevret, S., Hemmer, M., Carlet, J., & Langer, M. (1993). Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. *Intensive Care Med*, 19(5), 256-264.
- Chung, K., & Chang, A. (2002). Therapy for cough: active agents. *Pulm Pharmacol Ther*, 15(3), 335-338.
- Cichero, J. A., Heaton, S., & Bassett, L. (2009). Triaging dysphagia: nurse screening for dysphagia in an acute hospital. *Journal of clinical nursing*, 18(11), 1649-1659.
- Colice, G. L. (1992). Resolution of laryngeal injury following translaryngeal intubation. *Am Rev Respir Dis*, 145(2 Pt 1), 361-364.
- Colice, G. L., Stukel, T. A., & Dain, B. (1989). Laryngeal complications of prolonged intubation. *Chest*, 96(4), 877-884.
- Colodny, N. (2002). Interjudge and intrajudge reliabilities in fiberoptic endoscopic evaluation of swallowing (fees) using the penetration-aspiration scale: a replication study. *Dysphagia*, 17(4), 308-315. doi:10.1007/s00455-002-0073-4

- Colton House, J., Noordzij, J. P., Murgia, B., & Langmore, S. (2011). Laryngeal injury from prolonged intubation: a prospective analysis of contributing factors. *Laryngoscope*, 121(3), 596-600. doi:10.1002/lary.21403
- Cosgrove, J. F., & Carrie, S. (2015). Indications for and management of tracheostomies. *Surgery (Oxford)*, 33(4), 172-179.
- Daly, E., Miles, A. C., Scott, S., & Gillham, M. (2016). Finding the red flags: Swallowing difficulties after cardiac surgery in patients with prolonged intubation. *J Crit Care*, 31(1), 119-124.
- Daniels, S. K., Anderson, J. A., & Willson, P. C. (2012). Valid Items for Screening Dysphagia Risk in Patients With Stroke A Systematic Review. *Stroke*, 43(3), 892-897.
- Daniels, S. K., & Huckabee, M.-L. (2014). Dysphagia Following Stroke. 376.
- Davenport, P. M., Sapienza, C., & Bolser, D. (2002). Psychophysical assessment of the urge-to-cough. *European Respiratory Review*, 12(85), 249-253.
- Davenport, P. W., Vovk, A., Duke, R. K., Bolser, D. C., & Robertson, E. (2009). The urge-to-cough and cough motor response modulation by the central effects of nicotine. *Pulm Pharmacol Ther*, 22(2), 82-89.
- Davies, S. E. (2016). *Predicting and preventing aspiration pneumonia in patients with acute stroke and dysphagia* (Doctoral thesis, University of Canterbury, Christchurch, New Zealand). Retrieved from <http://ir.canterbury.ac.nz/handle/10092/12608>
- Davis, L. A., & Thompson Stanton, S. (2004). Characteristics of dysphagia in elderly patients requiring mechanical ventilation. *Dysphagia*, 19(1), 7-14. doi:10.1007/s00455-003-0017-7

- de Camargo, F. P., Ono, J., Park, M., Caruso, P., & Carvalho, C. R. R. (2010). An evaluation of respiration and swallowing interaction after orotracheal intubation. *Clinics*, 65(9), 919-922. doi:10.1590/S1807-59322010000900015
- De Jonghe, B., Bastuji-Garin, S., Durand, M.-C., Malissin, I., Rodrigues, P., Cerf, C., . . . Sharshar, T. (2007). Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Critical Care Medicine*, 35(9).
- de Larminat, V., Montravers, P., Dureuil, B., & Desmots, J. M. (1995). Alteration in swallowing reflex after extubation in intensive care unit patients. *Crit Care Med*, 23(3), 486-490.
- DeVita, M. A., & Spierer-Rundback, L. (1990). Swallowing disorders in patients with prolonged orotracheal intubation or tracheostomy tubes. *Crit Care Med*, 18(12), 1328-1330.
- Devlin, J. W., and Russel J. Roberts. (2009). Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. *Critical Care Clinics*, 25(3), 431-449.
- Dicpinigaitis, P. V. (2003). Cough reflex sensitivity in cigarette smokers. *Chest*, 123(3), 685-688.
- Dicpinigaitis, P. V. (2007). Experimentally induced cough. *Pulm Pharmacol Ther*, 20(4), 319-324. doi:10.1016/j.pupt.2006.10.003
- Dicpinigaitis, P.V., Chang, A. L., Dicpinigaitis, A. J., & Negassa, A. (2016). Effect of e-Cigarette Use on Cough Reflex Sensitivity. *CHEST Journal*, 149(1), 161-165.
- Dicpinigaitis, P. V., & Rauf, K. (1998). The influence of gender on cough reflex sensitivity. *CHEST Journal*, 113(5), 1319-1321.
- DiLisio, R. P., Mazzeffi, M. A., Bodian, C. A., & Fischer, G. W. (2013). Vocal cord paralysis after aortic surgery. *J Cardiothorac Vasc Anesth*, 27(3), 522-527.

- Dodds, W. J. (1989). The physiology of swallowing. *Dysphagia*, 3(4), 171-178.
- Dong, H., Christopher W. Loomis, and Detlef Bieger. (2001). Vagal afferent input determines the volume dependence of rat esophageal motility patterns. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 281(1), G44-G53.
- Donzelli, J., Brady, S., Wesling, M., & Theisen, M. (2005). Effects of the removal of the tracheotomy tube on swallowing during the fiberoptic endoscopic exam of the swallow (FEES). *Dysphagia*, 20(4), 283-289. doi:10.1007/s00455-005-0027-8
- Donzelli, J., Wesling, M., Brady, S., & Craney, M. (2003). Predictive value of accumulated oropharyngeal secretions for aspiration during video nasal endoscopic evaluation of the swallow. *Annals of Otolaryngology, Rhinology and Laryngology*, 112(5), 469-475.
- Doty, R. W. (1951). Influence of stimulus pattern on reflex deglutition. *American Journal of Physiology*, 166(1), 142-158.
- Drakulovic, M. B., Torres, A., Bauer, T. T., Nicolas, J. M., Nogu  , S., & Ferrer, M. (1999). Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *The Lancet*, 354(9193), 1851-1858.
- Easterling, C. S., & Robbins, E. (2008). Dementia and dysphagia. *Geriatric Nursing*, 29(4), 275-285.
- Ebihara, T., Ebihara, S., Maruyama, M., Kobayashi, M., Itou, A., Arai, H., & Sasaki, H. (2006). A randomized trial of olfactory stimulation using black pepper oil in older people with swallowing dysfunction. *J Am Geriatr Soc*, 54(9), 1401-1406.
- El Solh, A., Okada, M., Bhat, A., & Pietrantonio, C. (2003). Swallowing disorders post orotracheal intubation in the elderly. *Intensive Care Med*, 29(9), 1451-1455. doi:10.1007/s00134-003-1870-4
- Elliott, D., Aitken, L. M., Bucknall, T. K., Seppelt, I. M., Webb, S. A., Weisbrodt, L., & McKinley, S. (2013). Patient comfort in the intensive care unit: a multicentre,

- binational point prevalence study of analgesia, sedation and delirium management. *Critical Care and Resuscitation*, 15(3), 213-219.
- Falconer, J. R., Wu, Z., Lau, H., Suen, J., Wang, L., Pottinger, S., . . . Swift, S. (2014). An Investigation into the Stability and Sterility of Citric Acid Solutions Used for Cough Reflex Testing. *Dysphagia*, 29(5), 622-628.
- Fantus, B. (1912). "Patent medicines"—the pharmacist's duty in regard to them. *Journal of the American Pharmaceutical Association*, 1(2), 104-108.
- Farrell, M. J., Cole, L. J., Chiapoco, D., Egan, G. F., & Mazzone, S. B. (2012). Neural correlates coding stimulus level and perception of capsaicin-evoked urge-to-cough in humans. *NeuroImage*, 61(4), 1324-1335.
- Ferraris, V. A., Ferraris, S. P., Moritz, D. M., & Welch, S. (2001). Oropharyngeal dysphagia after cardiac operations. *Ann Thorac Surg*, 71(6), 1792-1795; discussion 1796.
- Fife, T. A., Butler, S. G., Langmore, S. E., Lester, S., Wright, S. C., et al. (2015). Use of Topical Nasal Anesthetic During Fiberoptic Endoscopic Evaluation of Swallowing in Dysphagic Patients. *Annals of Otolaryngology, Rhinology and Laryngology*, 124(3), 206-211.
- Fontana, G. A., & Lavorini, F. (2006). Cough motor mechanisms. *Respir Physiol Neurobiol*, 152(3), 266-281.
- Fujimura, M., Kamio, Y., Kasahara, K., Bando, T., Hashimoto, T., & Matsuda, T. (1995). Prostanoids and cough response to capsaicin in asthma and chronic bronchitis. *European Respiratory Journal*, 8(9), 1499-1505.
- Fujimura, M., Kasahara, K., Kamio, Y., Naruse, M., Hashimoto, T., & Matsuda, T. (1996). Female gender as a determinant of cough threshold to inhaled capsaicin. *European Respiratory Journal*, 9(8), 1624-1626.

- Goldsmith, T. (2000). Evaluation and Treatment of Swallowing Disorders following Endotracheal Intubation and Tracheostomy. *International Anesthesiology Clinics*, 38(3), 219-242.
- Hafner, G., Neuhuber, A., Hirtenfelder, S., Schmedler, B., & Eckel, H. E. (2008). Fiberoptic endoscopic evaluation of swallowing in intensive care unit patients. *Eur Arch Otorhinolaryngol*, 265(4), 441-446. doi:10.1007/s00405-007-0507-6
- Hansson, L., Wollmer, P., Dahlback, M., & Karlsson, J. A. (1992). Regional Sensitivity of Human Airways to Capsaicin-induced Cough. *American Review of Respiratory Disorders*, 145, 1191-1195.
- Hasegawa, R., & Nishino, T. (1999). Temporal changes in airway protective reflexes elicited by an endotracheal tube in surgical patients anaesthetized with sevoflurane. *Eur J Anaesthesiol*, 16(2), 98-102. doi:10.1046/j.1365-2346.1999.00422.x
- Heffner, J. E. (2010). Swallowing Complications After Endotracheal Extubation : Moving From "Whether" to "How". *Chest*, 137, 509-510. doi:10.1378/chest.09-2477
- Hegland, K. W., Bolser, D. C., & Davenport, P. W. (2012). Volitional Control of Reflex Cough. *Journal of Applied Physiology*, 113(1), 39-46.
- Helmy, A., Vizcaychipi, M., & Gupta, A. (2007). Traumatic brain injury: intensive care management. *British journal of anaesthesia*, 99(1), 32-42.
- Herkel, T., Uvizl, R., Doubravska, L., Adamus, M., Gabrhelik, T., Htoutou Sedlakova, M., . . . Vancouver. (2016). Epidemiology of hospital-acquired pneumonia: Results of a Central European multicenter, prospective, observational study compared with data from the European region. *Biomedical Papers*.
- Hinchey, J. A., Shephard, T., Furie, K., Smith, D., Wang, D., & Tonn, S. (2005). Formal dysphagia screening protocols prevent pneumonia. *Stroke*, 36(9), 1972-1976. doi:10.1161/01.STR.0000177529.86868.8d

- Hogue, C. W., Lappas, G. D., Creswell, L. L., Ferguson, T. B., Sample, M., Pugh, D., . . . Lappas, D. G. (1995). Swallowing Dysfunction after Cardiac Operations: Associated adverse outcomes and risk factors including intraoperative transesophageal echocardiography. *Journal Thoracic and Cardiovascular Surgery*, 110(2), 517-522.
- Hovig, B. (1981). Lower respiratory tract infections associated with respiratory therapy and anaesthesia equipment. *The Journal of Hospital Infection*, 2(4), 301-315.
- Hudson, H. M., Daubert, C. R., & Mills, R. H. (2000). The interdependency of protein-energy malnutrition, aging, and dysphagia. *Dysphagia*, 15(1), 31038.
- Hunter, J. D. (2006). Ventilator associated pneumonia. *Postgrad Med J*, 82(965), 172-178. doi:10.1136/pgmj.2005.036905
- Hutchings, H., Eccles, R., Smith, A., & Jawad, M. (1993). Voluntary cough suppression as an indication of symptom severity in upper respiratory tract infections. *European Respiratory Journal*, 6(10), 1449-1454.
- Irwin, R. S., Baumann, M. H., Bolser, D. C., Boulet, L.-P., Braman, S. S., Brightling, C. E., . . . Diczpinigaitis, P. V. (2006). Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *CHEST Journal*, 129(1_suppl), 1S-23S.
- Ji, R., Shen, H., Pan, Y., Wang, P., Liu, G., Wang, Y., . . . Wang, Y. (2013). Novel risk score to predict pneumonia after acute ischemic stroke. *Stroke*, 44(5), 1303-1309.
- Jin, Y. K., Kyoung, H. C., Gi, J. Y., Min, Y. K., & Ju, S. R. (2012). Does Removal of Tracheostomy Affect Dysphagia? A Kinematic Analysis. *Dysphagia*. doi:10.1007/s00455-012-9396-y
- Johnson, P. E., Belafsky, P. C., & Postma, G. N. (2003). Topical nasal anesthesia and laryngopharyngeal sensory testing: a prospective, double-blind crossover study. *Annals of Otology, Rhinology & Laryngology*, 112(1), 14-16.

- Kalf, J., De Swart, B., Bloem, B., & Munneke, M. (2012). Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. *Parkinsonism & related disorders*, 18(4), 311-315.
- Kamei, J. (1996). Role of Opioidergic and Serotonergic Mechanisms in Cough and Antitussives. *Pulm Pharmacol*, 9(5-6), 349-356.
doi:<http://dx.doi.org/10.1006/pulp.1996.0046>
- Kastanos, N., Miro, R. E., Perez, A. M., Mir, A. X., & Agusti-Vidal, A. (1983). Laryngotracheal injury due to endotracheal intubation: incidence, evolution, and predisposing factors. A prospective long-term study. *Critical Care Medicine*, 11(5), 362-367.
- Kelly, A. M., Leslie, P., Beale, T., Payten, C., & Drinnan, M. J. (2006). Fibreoptic endoscopic evaluation of swallowing and videofluoroscopy: does examination type influence perception of pharyngeal residue severity? *Clinical Otolaryngology*, 31(5).
- Kelly, H. E., Shaw, G. M., Brett, C. N., Greenwood, F. M., & Huckabee, M. L. (2016). The effect of titrated fentanyl on suppressed cough reflex in healthy adult volunteers. *Anaesthesia*, 71, 529-534.
- Kertscher, B., Speyer, R., Palmieri, M., & Plant, C. (2014). Bedside screening to detect oropharyngeal dysphagia in patients with neurological disorders: an updated systematic review. *Dysphagia*, 29(2), 204-212.
- Kessler, J. P., & Jean, A. (1985). Identification of the Medullary Swallowing Regions in the Rat. *Experimental Brain Research*, 57(2), 256-263.
- Kollarik, M., & Undem, B. J. (2006). Sensory transduction in cough-associated nerves. *Respir Physiol Neurobiol*, 152(3), 243-254. doi:10.1016/j.resp.2005.12.008
- Kollef, M. H. (1993). Ventilator-associated pneumonia: a multivariate analysis. *JAMA*, 270(16), 1965-1970.

- Kwok, A. M., Davis, J. W., Cagle, K. M., Sue, L., & Kaups, K. L. (2013). Post-extubation dysphagia in trauma patients: it's hard to swallow. *The American Journal of Surgery*, 206(6), 924-928.
- Lamvik, K. M. (2016). Modulation of spontaneous and volitional swallowing: Methodological and behavioural analyses. (Doctoral thesis, University of Canterbury, Christchurch, New Zealand). Retrieved from <http://ir.canterbury.ac.nz/handle/10092/12044>
- Langmore, S. E., Schatz, K., & Olsen, N. (1988). Fiberoptic endoscopic examination of swallowing safety: a new procedure. *Dysphagia*, 2(4), 216-219.
- Leder, S. B., Cohn, S. M., & Moller, B. A. (1998). Fiberoptic endoscopic documentation of the high incidence of aspiration following extubation in critically ill trauma patients. *Dysphagia*, 13(4), 208-212.
- Leder, S. B., & Murray, J. T. (2008). Fiberoptic endoscopic evaluation of swallowing. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 787-801.
- Leder, S. B., & Ross, D. A. (2010). Confirmation of No Causal Relationship Between Tracheotomy and Aspiration Status: A Direct Replication Study. *Dysphagia*, 25, 35-39. doi:10.1007/s00455-009-9226-z
- Leder, S. B., Ross, D. A., Briskin, K. B., & Sasaki, C. T. (1997). A Prospective, Double-Blind, Randomized Study on the Use of a Topical Anesthetic, Vasoconstrictor, and Placebo During Transnasal Flexible Fiberoptic Endoscopy. *Journal of Speech, Language, and Hearing Research*, 40(6), 1352-1357.
- Lee, P. C. L., Cotterill-Jones, C., & Eccles, R. (2002). Voluntary control of cough. *Pulm Pharmacol Ther*, 15(3), 317-320.
- Lee, C. W. S., & Ho, K. (2013). Sex differences in opioid analgesia and addiction: interactions among opioid receptors and estrogen receptors. *Molecular pain*, 9(1), 1.

- Lee, J. Y., Kim, D.-K., Seo, K. M., & Kang, S. H. (2014). Usefulness of the simplified cough test in evaluating cough reflex sensitivity as a screening test for silent aspiration. *Annals of rehabilitation medicine*, 38(4), 476-484.
- Lee, M. G., & Undem, B. J. (2008). Basic mechanisms of cough: current understanding and remaining questions. *Lung*, 186(1), 10-16.
- Leijten, F., & De Weerd, A. (1994). Critical illness polyneuropathy a review of the literature, definition and pathophysiology. *Clinical neurology and neurosurgery*, 96(1), 10-19.
- Leow, L. P., Beckert, L., Anderson, T., & Huckabee, M.-L. (2012). Changes in chemosensitivity and mechanosensitivity in aging and Parkinson's disease. *Dysphagia*, 27(1), 106-114.
- Lester, S., Langmore, S. E., Lintzenich, C. R., Wright, S. C., Grace - Martin, K., Fife, T., & Butler, S. G. (2013). The effects of topical anesthetic on swallowing during nasoendoscopy. *Laryngoscope*, 123(7), 1704-1708.
- Levine, S., Nguyen, T., Taylor, N., Friscia, M. E., Budak, M. T., Rothenberg, P., . . . Shrager, J. B. (2008). Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*, 358(13), 1327-1335. doi:10.1056/NEJMoa070447
- Lew, C. C. H., Yandell, R., Fraser, R. J., Chua, A. P., Chong, M. F. F., & Miller, M. (2016). Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit A Systematic Review. *Journal of Parenteral and Enteral Nutrition*. doi:0148607115625638
- Lewis, S. C., Li, L., Murphy, M. V., & Klompas, M. (2014). Risk factors for ventilator-associated events: a case-control multivariable analysis. *Critical Care Medicine*, 42(8), 1839-1848.

- Li, J., & Fine, J. (2004). On sample size for sensitivity and specificity in prospective diagnostic accuracy studies. *Statistics in Medicine*, 23(16), 2537-2550. doi:10.1002/sim.1836
- Logemann, J. A. (1998). *Evaluation and Treatment of Swallowing Disorders* (2 ed.). Austin, TX: Pro-Ed.
- Ludlow, C. L., Humbert, I., Saxon, K., Poletto, C., Sonies, B., & Crujido, L. (2007). Effects of surface electrical stimulation both at rest and during swallowing in chronic pharyngeal dysphagia. *Dysphagia*, 22(1), 1-10.
- Macht, M., Wimbish, T., Bodine, C., & Moss, M. (2013). ICU-acquired swallowing disorders. *Critical Care Medicine*, 41(10), 2396-2405.
- Macht, M., Wimbish, T., Clark, B. J., Benson, A. B., Burnham, E. J., Williams, A., & Moss, M. (2011). Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. *Critical Care*, 15, 1-9.
- Macht, M., Wimbish, T., Clark, B. J., Benson, A. B., Burnham, E. L., Williams, A., & Moss, M. (2012). Diagnosis and treatment of post-extubation dysphagia: results from a national survey. *J Crit Care*, 27(6), 578-586. doi:10.1016/j.jcrc.2012.07.016
- Mackay, L. E., Morgan, A. S., & Bernstein, B. A. (1999). Swallowing disorders in severe brain injury: risk factors affecting return to oral intake. *Arch Phys Med Rehabil*, 80(4), 365-371.
- Malandraki, G. A., Markaki, V., Georgopoulos, V. C., Psychogios, L., & Nanasc, S. (2016). Postextubation Dysphagia in Critical Patients: A First Report From the Largest Step-Down Intensive Care Unit in Greece. *American Journal of Speech-Language Pathology*, 25(2), 150-156.

- Mann, G., Hankey, G. J., & Cameron, D. (2000). Swallowing disorders following acute stroke: prevalence and diagnostic accuracy. *Cerebrovascular Diseases*, 10(5), 380-386.
- Marik, P. E. (2001). Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*, 344(9), 665-671. doi:10.1056/NEJM200103013440908
- Martin-Harris, B., & Jones, B. (2008). The videofluorographic swallowing study. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 769-785.
- Martino, R., Foley, N., Bhogal, S., Diamant, N., Speechley, M., & Teasell, R. (2005). Dysphagia after stroke incidence, diagnosis, and pulmonary complications. *Stroke*, 36(12), 2756-2763.
- Matsuo, K. P., Jeffrey. (2008). Anatomy and Physiology of Feeding and Swallowing: Normal and Abnormal. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 691-707.
- Mazzone, S. B. (2005). An overview of the sensory receptors regulating cough. *Cough*, 1, 2. doi:10.1186/1745-9974-1-2
- Mazzone, S. B., Cole, L. J., Ando, A., Egan, G. F., & Farrell, M. J. (2011). Investigation of the neural control of cough and cough suppression in humans using functional brain imaging. *J Neurosci*, 31(8), 2948-2958. doi:10.1523/JNEUROSCI.4597-10.2011
- Mazzone, S. B., McGovern, A. E., Koo, K., & Farrell, M. J. (2009). Mapping supramedullary pathways involved in cough using functional brain imaging: comparison with pain. *Pulm Pharmacol Ther*, 22(2), 90-96. doi:10.1016/j.pupt.2008.08.003
- Mazzone, S. B., McLennan, L., McGovern, A. E., Egan, G. F., & Farrell, M. J. (2007). Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med*, 176(4), 327-332. doi:10.1164/rccm.200612-1856OC

- Mazzone, S. B., Mori, N., & Canning, B. J. (2005). Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. *J Physiol*, 569(Pt 2), 559-573. doi:10.1113/jphysiol.2005.093153
- McCullough, G., Wertz, R., & Rosenbek, J. (2001). Sensitivity and specificity of clinical/bedside examination signs for detecting aspiration in adults subsequent to stroke. *Journal of communication disorders*, 34(1), 55-72.
- McNicol, E. D., Ferguson, M. C., & Hudcova, J. (2015). Patient controlled opioid analgesia versus non - patient controlled opioid analgesia for postoperative pain. *The Cochrane Library*.
- Miles, & Huckabee, M. L. (2013). Intra- and Inter-rater Reliability for Judgement of Cough Following Citric Acid Inhalation. *International Journal of Speech-Language Pathology*, 15(2), 209-215.
- Miles, Moore, S., McFarlane, M., Lee, F., Allen, J., & Huckabee, M. L. (2013). Comparison of cough reflex test against instrumental assessment of aspiration. *Physiology & Behavior*, 118, 25-31.
- Miles, Zeng, I. S., McLauchlan, H., & Huckabee, M. L. (2013). Cough reflex testing in Dysphagia following stroke: a randomized controlled trial. *J Clin Med Res*, 5(3), 222-233. doi:10.4021/jocmr1340w
- Miles, A. C. (2013). *Cough Reflex Testing in Acute Dysphagia Management: Validity, Reliability and Clinical Application* (Doctoral thesis, University of Canterbury, Christchurch, New Zealand). Retrieved from <http://ir.canterbury.ac.nz/handle/10092/8357>
- Miller, A. J. (2008). The Neurobiology of Swallowing and Dysphagia *Developmental Disabilities Research Reviews*, 14(2), 77-86.
- Monroe, M. D., Huckabee, M. L., & Robb, M. (2010). *Citric acid inhalation cough challenge*

- Establishing normative data* (Masters thesis, University of Canterbury, Christchurch, New Zealand). Retrieved from <http://www.ir.canterbury.ac.nz/handle/10092/4149>
- Monroe, M. D., Manco, K., Bennett, R., & Huckabee, M. L. (2014). Citric acid cough reflex test: Establishing normative data. *Speech, Language & Hearing, 17*(4), 216-224.
- Morice, A. H.. (1996). Inhalation Cough Challenge in the Investigation of the Cough Reflex and Antitussives. *Pulm Pharmacol, 9*(5–6), 281-284.
doi:<http://dx.doi.org/10.1006/pulp.1996.0036>
- Morice, A. H., Fontana, G. A., Belvisi, M. G., Birring, S. S., Chung, K. F., Dicpinigaitis, P. V., . . . Widdicombe, J. (2007a). ERS guidelines on the assessment of cough. *Eur Respir J, 29*(6), 1256-1276. doi:10.1183/09031936.00101006
- Morice, A. H., Higgins, K., & Yeo, W. (1992). Adaptation of cough reflex with different types of stimulation. *European Respiratory Journal, 5*(7), 841-847.
- Morice, A. H., Kastelik, J. A., & Thompson, R. J. (2000). Gender differences in airway behaviour. *Thorax, 55*(7), 628-628.
- Morice, A. H., Kastelik, J. A., & Thompson, R. (2001). Cough challenge in the assessment of cough reflex. *Br J Clin Pharmacol, 52*(4), 365-375.
- Morice, A. H., Menon, M. S., Mulrennan, S. A., Everett, C. F., Wright, C., Jackson, J., & Thompson, R. (2007b). Opiate Therapy in Chronic Cough. *Am J Respir Crit Care Med, 175*(4), 312-315.
- Murray, J., Langmore, S., Ginsberg, S., & Dostie, A. (1996). The significance of accumulated oropharyngeal secretions and swallowing frequency in predicting aspiration. *Dysphagia, 11*(2), 99-103. doi:10.1007/bf00417898
- Nakajoh, K., Nakagawa, T., Sekizawa, K., Matsui, T., Arai, H., & Sasaki, H. (2000). Relation between incidence of pneumonia and protective reflexes in post-stroke patients with oral or tube feeding. *J Intern Med, 247*(1), 39-42.

- Nakazawa, H., Sekizawa, K., Ujiie, Y., Sasaki, H., & Takishima, T. (1993). Risk of aspiration pneumonia in the elderly. *Chest*, 103(5), 1636-1637.
- Narula, M., McGovern, A. E., Yang, S.-K., Farrell, M. J., & Mazzone, S. B. (2014). Afferent neural pathways mediating cough in animals and humans. *Journal of thoracic disease*, 6(Suppl 7), S712-719.
- Nejla, S., Fujimura, M., & Kamio, Y. (2000). Comparison between tidal breathing and dosimeter methods in assessing cough receptor sensitivity to capsaicin. *Respirology*, 5(4), 337-342.
- Nishino, T. (2013). The swallowing reflex and its significance as an airway defensive reflex. *Frontiers in Physiology*, 3, 489.
- Noordally, S. O., Sohawon, S., De Gieter, M., Bellout, H., & Verougstraete, G. (2011). A Study to Determine the Correlation Between Clinical, Fiber-Optic Endoscopic Evaluation of Swallowing and Videofluoroscopic Evaluations of Swallowing After Prolonged Intubation. *Nutrition in Clinical Practice*, 26(457-462), 457. doi:10.1177/0884533611413769
- Nordang, L., Lindholm, C. E., Larsson, J., & Linder, A. (2016). Early laryngeal outcome of prolonged intubation using an anatomical tube: a double blind, randomised study. *European Archives of Oto-Rhino-Laryngology*, 273(3), 703-708.
- O'Dea, M. B., Langmore, S. E., Krisciunas, G. P., Walsh, M., Zanchetti, L. L., et al. (2015). Effect of Lidocaine on Swallowing During FEES in Patients with Dysphagia. *Annals of Otology, Rhinology and Laryngology*, 124(7), 537-544.
- O'Donoghue, S., & Bagnall, A. (1999). Videofluoroscopic evaluation in the assessment of swallowing disorders in paediatric and adult populations. *Folia phoniatrica et logopaedica*, 51(4-5), 158-171.

- Padovani, A. R., Moraes, D. P., de Medeiros, G. C., de Almeida, T. M., & de Andrade, C. R. F. (2008). Orotracheal intubation and dysphagia: comparison of patients with and without brain damage. *einstein*, 6(3), 343-349.
- Park, Y.-H., Han, H.-R., Oh, B.-M., Lee, J., Park, J.-a., Yu, S. J., & Chang, H. (2013). Prevalence and associated factors of dysphagia in nursing home residents. *Geriatric Nursing*, 34(3), 212-217.
- Pecova, R., Javorkova, N., Kudlicka, J., & Tatar, M. (2007). TUSSIGENIC AGENTS IN THE MEASUREMENT. *Journal of Physiology and Pharmacology*, 58(5), 531-538.
- Peppard, S. B., & Dickens, J. H. (1983). Laryngeal injury following short-term intubation. *Ann Otol Rhinol Laryngol*, 92(4 Pt 1), 327-330.
- Peterson, S. J., Tsai, A. A., Scala, C. M., Sowa, D. C., Sheean, P. M., & Braunschweig, C. L. (2010). Adequacy of oral intake in critically ill patients 1 week after extubation. *Journal of the American Dietetic Association*, 110(3), 427-433.
- Pinto, A., Yanai, M., Sekizawa, K., Aikawa, T., & Sasaki, H. (1995). Conditioned enhancement of cough response in awake guinea pigs. *International archives of allergy and immunology*, 108(1), 95-98.
- Pitts, T., Rose, M. J., Mortensen, A. N., Poliacek, I., Sapienza, C. M., Lindsey, B. G., . . . Bolser, D. C. (2013). Coordination of cough and swallow: a meta-behavioral response to aspiration. *Respir Physiol Neurobiol*, 189(3), 543-551.
- Pizzorni, N., Ginocchio, D., Mozzanica, F., Roncoroni, L., Scarponi, L., & Schindler, A. (2014). Head and neck diseases and disorders causing oropharyngeal dysphagia. *Journal of Gastroenterology and Hepatology Research*, 3(10), 1272-1280.
- Ponfick, M., Linden, R., & Nowak, D. A. (2015). Dysphagia—A common, transient symptom in critical illness polyneuropathy: a fiberoptic endoscopic evaluation of swallowing study. *Critical Care Medicine*, 43(2), 365-372.

- Postma, G. N., McGuirt, W. F., Sr., Butler, S. G., Rees, C. J., Crandall, H. L., & Tansavatdi, K. (2007). Laryngopharyngeal abnormalities in hospitalized patients with dysphagia. *Laryngoscope*, 117(10), 1720-1722. doi:10.1097/MLG.0b013e31811ff906
- Potts, R. G., Zaroukian, M. H., Guerrero, P. A., & Baker, C. D. (1993). Comparison of blue dye visualization and glucose oxidase test strip methods for detecting pulmonary aspiration of enteral feedings in intubated adults. *Chest*, 103(1), 117-121.
- Pounsford, J., & Saunders, K. (1985). Diurnal variation and adaptation of the cough response to citric acid in normal subjects. *Thorax*, 40(9), 657-661.
- Ramsey, D. J., Smithard, D. G., & Kalra, L. (2003). Early assessments of dysphagia and aspiration risk in acute stroke patients. *Stroke*, 34(5), 1252-1257.
- Rao, N., Brady, S. L., Chaudhuri, G. D., J.J., & Wesling, M. W. (2003). Gold-standard? Analysis of the videofluoroscopic and fiberoptic endoscopic swallow examinations. *Journal of Applied Research*, 3(1), 1-8.
- Redington, A. E., Morice, A. H., & Kastelik, J. A. (2005). Acid Inhalation Cough Challenge *Acute and Chronic Cough* (pp. 177-194): CRC Press.
- Reinarz, J. A., Pierce, A. K., Mays, B. B., & Sanford, J. P. (1965). The potential role of inhalation therapy equipment in nosocomial pulmonary infection. *The Journal of Clinical Investigation*(44), 831-839.
- U. S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. (2002). Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation. Retrieved from <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf>

- Robbins, J., Kays, S. A., Gangnon, R. E., Hind, J. A., Hewitt, A. L., Gentry, L. R., & Taylor, A. J. (2007). The effects of lingual exercise in stroke patients with dysphagia. *Arch Phys Med Rehabil*, 88(2), 150-158.
- Rosenbek, J. C., Robbins, J. A., Roecker, E. B., Coyle, J. L., & Wood, J. L. (1996). A penetration-aspiration scale. *Dysphagia*, 11(2), 93-98.
- Rousou, J. A., Tighe, D. A., Garb, J. L., Krasner, H., Engelman, R. M., Flack, J. E., 3rd, & Deaton, D. W. (2000). Risk of dysphagia after transesophageal echocardiography during cardiac operations. *Ann Thorac Surg*, 69(2), 486-489; discussion 489-490.
- Safdar, N., Dezfulian, C., Collard, H. R., & Saint, S. (2005). Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med*, 33(10), 2184-2193.
- Saunders, J., & Smith, T. (2010). Malnutrition: causes and consequences. *Clinical Medicine*, 10(6), 624-627.
- Scannapieco, F. A. (2006). Pneumonia in nonambulatory patients: the role of oral bacteria and oral hygiene. *The American Dental Association*, 137, S21-S25.
- Schatz, K., Langmore, S., & Olsen, N. (1991). Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. *Otology, Rhinology & Laryngology*, 100(8), 678-681.
- Scheel, R., Pisegna, J. M., McNally, E., Noordzij, J. P., & Langmore, S. E. (2016). Endoscopic Assessment of Swallowing After Prolonged Intubation in the ICU Setting. *Annals of Otology, Rhinology and Laryngology*, 125(1), 43-52.
- Schenning, K. J., & Deiner, S. G. (2015). Postoperative delirium: a review of risk factors and tools of prediction. *Current Anesthesiology Reports*, 5(1), 48-56.
- Schröter-Morasch, H., Bartolome, G., Troppmann, N., & Ziegler, W. (1999). Values and limitations of pharyngolaryngoscopy (transnasal, transoral) in patients with dysphagia. *Folia phoniatrica et logopaedica*, 51(4-5), 172-182.

- Sekizawa, K., Ujiie, Y., Itabashi, S., Sasaki, H., & Takishima, T. (1990). Lack of cough reflex in aspiration pneumonia. *Lancet*, 335(8699), 1228-1229.
- Selim, M. (2007). Perioperative Stroke. *New England Journal of Medicine*, 356(7), 706-713.
- Shannon, R., Baekey, D. M., Morris, K. F., Nuding, S. C., Segers, L. S., & Lindsey, B. G. (2004). Production of reflex cough by brainstem respiratory networks. *Pulm Pharmacol Ther*, 17(6), 369-376. doi:10.1016/j.pupt.2004.09.022
- Shehabi, Y., Bellomo, R., Reade, M. C., Bailey, M., Bass, F., Howe, B., . . . Webb, S. (2013). Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study. *Critical Care Medicine*, 41(8), 1983-1991.
- Sider, L., Mintzer, R. A., Deschler, T. W., Kim, K. S., & Weinberg, P. E. (1983). Control of swallowing by use of topical anesthesia during digital subtraction angiography. *Radiology*, 148(2), 563-564.
- Simpson, H., Clancy, M., Goldfrad, C., & Rowan, K. (2005). Admissions to intensive care units from emergency departments: a descriptive study. *Emergency Medicine Journal*, 22(6), 423-428.
- Sitkauskiene, B., & Dicpinigaitis, P. V. (2010). Effect of smoking on cough reflex sensitivity in humans. *Lung*, 188(1), 29-32.
- Sitkauskiene, B., Stravinskaite, K., Sakalauskas, R., & Dicpinigaitis, P. V. (2007). Changes in cough reflex sensitivity after cessation and resumption of cigarette smoking. *Pulm Pharmacol Ther*, 20(3), 240-243.
- Skoretz, S. A., Flowers, H. L., & Martino, R. (2010). The incidence of dysphagia following endotracheal intubation: a systematic review. *Chest*, 137(3), 665-673. doi:10.1378/chest.09-1823

- Soh, S., Park, W. K., Kang, S. W., Lee, B. R., & Lee, J. R. (2014). Sex differences in remifentanyl requirements for preventing cough during anesthetic emergence. *Yonsei medical journal*, 55(3), 807-814.
- Stauffer, J. L., Olson, D. E., & Petty, T. L. (1981). Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. *Am J Med*, 70(1), 65-76.
- Steele, C. M., Bailey, G. L., Chau, T., Molfenter, S. M., Oshalla, M., Waito, A. A., & Zoratto, D. C. (2011). The relationship between hyoid and laryngeal displacement and swallowing impairment. *Clinical Otolaryngology*, 36(1), 30-36.
- Steele, C. M., & Miller, A. J. (2010). Sensory input pathways and mechanisms in swallowing: a review. *Dysphagia*, 25(4), 323-333. doi:10.1007/s00455-010-9301-5
- Stephens, R. E., Addington, W. R., & Widdicombe, J. G. (2003). Effect of acute unilateral middle cerebral artery infarcts on voluntary cough and the laryngeal cough reflex. *American journal of physical medicine & rehabilitation*, 82(5), 379-383.
- Sugiyama, Y., Shiba, K., Nakazawa, K., Suzuki, T., Umezaki, T., Ezure, K., . . . Hisa, Y. (2011). Axonal projections of medullary swallowing neurons in guinea pigs. *Journal of Comparative Neurology*, 519(11), 2193-2211.
- Tadie, J. M., Behm, E., Lecuyer, L., Benhmamed, R., Hans, S., Brasnu, D., . . . Guerot, E. (2010). Post-intubation laryngeal injuries and extubation failure: a fiberoptic endoscopic study. *Intensive Care Med*, 36(6), 991-998. doi:10.1007/s00134-010-1847-z
- Tanaka, A., Isono, S., Ishikawa, T., & Nishino, T. (2005). Laryngeal reflex before and after placement of airway interventions: endotracheal tube and laryngeal mask airway. *Anesthesiology*, 102(1), 20-25.

- Teismann, I. K., Steinstraeter, O., Stoeckigt, K., Suntrup, S., Wollbrink, A., Pantev, C., & Dziewas, R. (2007). Functional oropharyngeal sensory disruption interferes with the cortical control of swallowing. *BMC Neurosci*, 8, 62. doi:10.1186/1471-2202-8-62
- Terzano, C., Petroianni, A., Parola, D., & Ricci, A. (2007). Compressor/nebulizers differences in the nebulization of corticosteroids. The CODE study (Corticosteroids and Devices Efficiency). *European review for medical and pharmacological sciences*, 11(4), 225.
- Tolep, K., Getch, C. L., & Criner, G. J. (1996). Swallowing dysfunction in patients receiving prolonged mechanical ventilation. *Chest*, 109(1), 167-172.
- Ushioda, T., Watanabe, Y., Sanjo, Y., Yamane, G.-y., Abe, S., Tsuji, Y., & Ishiyama, A. (2012). Visual and auditory stimuli associated with swallowing activate mirror neurons: a magnetoencephalography study. *Dysphagia*, 27(4), 504-513.
- Van Daele, D. J., McCulloch, T. M., Palmer, P. M., & Langmore, S. E. (2005). Timing of glottic closure during swallowing: a combined electromyographic and endoscopic analysis. *Annals of Otology, Rhinology & Laryngology*, 114(6), 478-487.
- Vila, J., Bosque, M. D., Garcia, M., Palomar, M., Quesada, P., & Ramis, B. (1997). Endoscopic evolution of laryngeal injuries caused by translaryngeal intubation. *Eur Arch Otorhinolaryngol*, 254 Suppl 1, S97-100.
- Wakasugi, Y., Tohara, H., Hattori, F., Motohashi, Y., Nakane, A., Goto, S., . . . Uematsu, H. (2008). Screening test for silent aspiration at the bedside. *Dysphagia*, 23(4), 364-370. doi:10.1007/s00455-008-9150-7
- Wakasugi, Y., Tohara, H., Nakane, A., Murata, S., Mikushi, S., Susa, C., . . . Uematsu, H. (2014). Usefulness of a handheld nebulizer in cough test to screen for silent aspiration. *Odontology*, 102(1), 76-80.

- Wang, C. M., Shieh, W. Y., Chen, J. Y., & Wu, Y. R. (2015). Integrated non - invasive measurements reveal swallowing and respiration coordination recovery after unilateral stroke. *Neurogastroenterology & Motility*, 27(10), 1398-1408.
- Warnecke, T. (2009). The safety of fiberoptic endoscopic evaluation of swallowing in acute stroke patients. *Stroke*, 40(2), 482-486.
- Watando, A., Ebihara, S., Ebihara, T., Okazaki, T., Takahashi, H., Asada, M., & Sasaki, H. (2004). Daily oral care and cough reflex sensitivity in elderly nursing home patients. *CHEST Journal*, 126(4), 1066-1070.
- Weinstein, R. A., Bonten, M. J., Kollef, M. H., & Hall, J. B. (2004). Risk factors for ventilator-associated pneumonia: from epidemiology to patient management. *Clinical Infectious Diseases*, 38(8), 1141-1149.
- Weissman, C. (1999). Pulmonary function after cardiac and thoracic surgery. *Anesthesia & Analgesia*, 88(6), 1272-1279.
- Whited, R. E. (1984). A prospective study of laryngotracheal sequelae in long-term intubation. *Laryngoscope*, 94(3), 367-377.
- Widdicombe, J., Addington, W. R., Fontana, G. A., & Stephens, R. E. (2011). Voluntary and reflex cough and the expiration reflex; implications for aspiration after stroke. *Pulm Pharmacol Ther*, 24(3), 312-317. doi:10.1016/j.pupt.2011.01.015
- Widdicombe, J., Eccles, R., & Fontana, G. (2006). Supramedullary influences on cough. *Respir Physiol Neurobiol*, 152(3), 320-328. doi:10.1016/j.resp.2006.02.018
- Widdicombe, J. (2001). Airway receptors. *Respir Physiol*, 125(1-2), 3-15.
- Wong, C. H., Matai, R., & Morice, A. H. (1999). Cough induced by low pH. *Respir Med*, 93(1), 58-61.

Yamanda, S., Ebihara, S., Ebihara, T., Yamasaki, M., Asamura, T., Asada, M., . . . Arai, H.
(2008). Impaired urge-to-cough in elderly patients with aspiration pneumonia. *Cough*,
4, 11. doi:10.1186/1745-9974-4-11

APPENDICES

1. Protocol for Study I
2. Protocol for Study II

**A Prospective Study of Cough Response to Nebulised
Citric Acid following Intubation for Elective Cardiac
Surgery**

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Supported by:

**University of Canterbury and The New Zealand Brain Research
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Citric Acid Provided by:

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PRÉCIS

Study Title

A Prospective Study of Cough Response to Nebulised Citric Acid following
Intubation for Elective Cardiac Surgery

Objectives

The primary objective is to determine the relationship between orotracheal intubation and cough response to nebulized citric acid in patients who have undergone elective cardiothoracic surgery.

The secondary objective is to determine when, in 12-hour intervals, cough returns to pre-intubation baseline.

Participants

One hundred consecutive patients who meet the inclusion criteria.

Method

Consecutive subjects admitted for elective cardiovascular surgery will be enrolled in the study. The Coordinating Investigator (CI) will gather medical history from the medical record and patient interview. Any patient with a history of neurological disorder, medical condition or trauma involving the head or neck region or dysphagia will be excluded. Participants will receive written and verbal explanation of the project, including screening and enrollment process and criteria, and given the opportunity to consent.

Once enrolled, each subject will undergo a Cough Reflex Test (CRT) performed by the CI. The initial CRT will be performed before anaesthesia is administered for surgery. Cough testing is described in detail in section 5.1. Any subject with an absent cough in the pre-intubation testing will be excluded from the study.

The CRT will be repeated within two hours of extubation. All patients will have the CRT repeated twice daily, once between 0700 and 0900 and again between 1900 and 2100 until resolution of cough, discharge from hospital or death. Resolution of cough will be judged as a return to pre-intubation cough baseline performance. Patients will be excluded from analysis if they suffer a new neurological event, such as intra- or post-operative stroke. If a patient requires reintubation, this will be noted and the cough tests will resume after extubation. Patients that receive tracheostomies will be excluded from the study.

Outcome measures.

Dependent variable:

- Response to cough reflex test, classified as present or absent

Independent variable:

- Time from extubation

Covariates:

- Complication noted on intubation
- Type of endotracheal tube
- Age
- Gender
- Ethnicity

- Type and amount of anaesthesia used
- Surgery bypass time
- Length of intubation
- Length of stay in ICU

Statistical plan

Analyses will include binomial distribution and Kaplan-Meier Life Table as well as McNemar's test, Wilcoxon Sign Rank test, T-Test and the Cox Proportional Hazard Model.

1. STUDY OBJECTIVES

1.1 Primary Objective

To test the hypothesis that orotracheal intubation inhibits cough response to nebulised citric acid in neurologically intact adults undergoing intubation for elective cardiac surgery.

1.2 Secondary Objectives

To determine when, in 12-hour intervals, cough response returns to pre-intubation baseline. This data will be used to design a swallow screening protocol to be used with patients after extubation.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Each year in Capital & Coast Intensive Care Unit approximately 1200 patients are intubated. Dysphagia, or disordered swallowing, is common post-intubation with studies in the general ICU population indicating that over 50% of patients have some level of dysphagia soon after extubation. Up to one half of these patients aspirate "silently" or without overt evidence of aspiration, such as coughing. Patients who aspirate silently are particularly difficult to detect as ICU staff use the presence of coughing with food and drink to determine if patients have dysphagia. Currently, patients are only referred to speech-language therapy for a swallowing assessment if they demonstrate overt signs of aspiration and it is likely that many patients are allowed to eat and drink while silently aspirating. Aspiration can be a causal factor in the development of pneumonia, which is the most common nosocomial

infection in ICU. Development of pneumonia significantly increases length of stay, risk of death and cost of treatment (Safdar et al., 2005).

2.2 Study Rationale

Dysphagia and aspiration after orotracheal intubation in the Intensive Care Unit (ICU) population is common (Ajemian et al., 2001; de Larminat et al., 1995; El Solh et al., 2003; Macht et al., 2011; Noordally et al., 2011). Studies measuring frequency of aspiration in a general ICU population post-extubation indicate that it occurs in 27% to 56% of patients (Ajeman, El Solh, Noordally). Intensive care patients who aspirate are at increased risk of developing pneumonia. Pneumonia results in increased length of stay, mortality and cost of care (Safdar et al., 2005).

Recently extubated intensive care patients are particularly at risk for silent aspiration, which cannot be identified by bedside clinical assessment (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). Most studies that have looked specifically at silent aspiration report silent aspirators as a percentage of total aspirators, with rates ranging from 22% to 44% (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). Often these patients are allowed to eat and drink soon after extubation, potentially putting them at increased risk of aspirating.

Sensory testing of patients after orotracheal intubation suggests that airway reflexes are impaired in these patients in the short and medium term (Colice et al., 1989; Tanaka et al., 2005). Airway sensation in the recently extubated population has been tested by injection of water into the glottis (Tanaka), presence of a gag on laryngoscopy (Colice), and light touch to the aryepiglottic folds using a laryngoscope (Scheel).

The Cough Reflex Test (CRT) is emerging as a useful tool for testing subjects' ability to protect their airway through reflexive cough (Addington et al., 2005; Wakasugi et al., 2008). Currently, there is no evidence in the literature describing the use of CRT to test sensation after extubation. Most research relating cough reflex to safety during swallowing has been in the stroke population. Absent cough to CRT with acidic tussives (i.e. citric acid and tartaric acid) has high specificity as a predictor of aspiration pneumonia (Addington et al., 2005; Wakasugi et al., 2008). In 2005, Addington and colleagues reported on 818 consecutive stroke patients who all underwent CRT with tartaric acid before starting oral intake after acute stroke. Patients who failed the CRT were kept nil by mouth. Three and

one half percent of subjects with a normal response to CRT developed pneumonia during their hospital stay compared to 10% of subjects with a weak response to CRT and 16% of patients with an absent cough response (Addington et al., 2005). Research recently conducted in New Zealand by the supervisor of this project, Dr. Maggie-Lee Huckabee and Anna Miles (under review) showed a non-significant trend for an increase in mortality in patients with absent cough reflex. CRT with nebulized citric acid is gaining traction as a tool for dysphagia assessment in New Zealand, particularly with stroke patients.

Given that aspiration places ICU patients at risk of pneumonia, silent aspiration is common in patients after orotracheal intubation and CRT testing is a useful tool for determining risk of silent aspiration, it follows that it may be useful to use CRT with patients after orotracheal intubation to help determine safety of oral intake. However, we do not currently know if the cough reflex is often impaired after orotracheal intubation. This research study will test the hypothesis that that orotracheal intubation inhibits cough response to nebulised citric acid in neurologically intact adults undergoing intubation for elective cardiac surgery. It will also aim to determine when, in 12-hour intervals, most subjects' cough response returns to pre-intubation baseline. If the hypothesis is proven and patients do indeed have impaired cough reflex after extubation, the data will be used to design a swallow screening protocol to be used with patients after orotracheal intubation.

3. STUDY DESIGN

This is a prospective cohort observational study.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria below to participate in this study.

- 18 years of age or older
- Undergoing intubation for elective (non-urgent) coronary artery bypass grafting (CABG) without valve replacement

4.2 Exclusion Criteria

Participants meeting any of the exclusion criteria at baseline will be excluded from study participation.

- Presence or history of neurological disorder (e.g. stroke, Parkinson's, MS) documented as per medical records
- Presence or history of cancer of the head or neck documented in medical records
- Presence or history of oropharyngeal dysphagia documented in medical records or obtained in patient interview
- History of trauma to the neck documented in medical records
- Inability or unwillingness of individual to give written informed consent.

4.3 Study Enrollment Procedures

- The Cardiac Liaison Nurse will ensure all patients scheduled for elective CABG without valve replacement receive a one-page Introductory Letter (Appendix A) and Patient Information Sheet (Appendix B) by post with their pre-admission paperwork.
- During the admission process the ward clerk will ask each patient if they would be willing to speak to the CI about the study
- The CI will visit each patient who agrees and provide each candidate with written and verbal information about the study.
- Consenting participants will sign the Consent Form (Appendix C) and be recorded in the Participants Log (Appendix D).
- The CI will review the medical record and collect history from each participant to identify exclusion criteria.
- Patients who do not consent and those who are excluded from the study will be recorded in the Screening Log (Appendix E).

5. SCHEDULE OF EVALUATIONS

5.1 Baseline Assessment (CRT1)

Once a subject is enrolled a Cough Reflex Test (CRT) will occur immediately or no later than 30 minutes before delivery of anaesthesia. The procedure for CRT will be the same each time and is described below.

- The patient must be sitting up in a bed or chair for assessment with head raised

at least 60 degrees.

- In CRT1, up to three concentrations will be trialed. These are 0.4, 0.8 and 1.2 mol (diluted in .9% sodium chloride).
- In CRT1, the CI will first test with the lowest concentration of citric acid.
- Three to four milliliters of sterile citric acid solution will be placed in a nebulizer cup, which is attached by tubing to a DeVilbiss Pulmomate nebulizer with a free-flow rate of eight liters per minute.
- A facemask will be attached by connecting tubing to the nebulizer. The CI will place the facemask over the subject's nose and mouth and ask them to quietly breath for 15 seconds. The subject will be told that they should try not to cough.
- If the subject does cough at least twice on two of three trials the cough will be judged present. The CI will judge the cough to be present or absent and record the result on the Case Report Form E).
- The citric acid test will be followed by one trial with normal saline water. If the patient coughs with normal saline, the cough will be considered abnormal and the patient will be excluded from the study. The results will be recorded on the case report sheet and saved with the study records.
- If the subject's cough is present on the first concentration of citric acid and absent on the saline solution the test is complete.
- If the subject's cough is absent, the test will be repeated with the next concentration (0.8 mol). Testing will continue with a third concentration (1.2 mol) if needed.
- The CRT will always end with a trial of saline. Their results will be recorded on the case report sheet and saved with the study records.
- Subjects who do not cough on any concentration will be considered abnormal and their data will not be included in the study. Their results will be recorded on the case report sheet and saved with the study records.

5.2 Follow-up Assessments

The CI will repeat the CRT within two hours of extubation (CRT2). Extubation may occur the day of surgery or up to several days later. ICU nursing staff will phone the CI when planning extubation. CRT2 will follow the procedure exactly as described above, except will start with the concentration that successfully prompted a cough at baseline (CRT1) and then increase in concentration as needed. The same concentrations of citric acid will be used. These are 0.4, 0.8 and 1.2 mol. The CI will again rate each cough as present or absent and record the results on the Case Report Form.

Subjects with a cough present at their baseline threshold or lower will have completed the study. Subjects with an absent cough or a higher threshold will have a repeat CRT twice daily until they achieve a pass at their baseline threshold. The CI will perform repeat CRT tests twice daily, the first between 0730 and 0930 and the second between 1930 and 2130. Testing will continue for each patient according to this schedule until they pass with a strong cough, are discharged from hospital or die. If a patient dies before CRT2, their data will not be included in analysis. If they die after CRT2 their data will be included in analysis.

Subjects who receive a tracheostomy will be excluded from the study at the time the tracheostomy is inserted. Subjects who suffer a new neurological event, such as intra-operative stroke, will continue in the study, but their data will be analysed separately. A suspected or confirmed neurological event documented in the medical record by the Intensive Care physician or cardiothoracic surgeon will constitute a new neurological event.

6. SAFETY ASSESSMENTS/ADVERSE EVENTS

An adverse event is defined as any unfavorable and unintended diagnosis, symptom, sign syndrome or disease that is not related to the subject's medical condition. The CI does not anticipate adverse events. Subjects may experience a choking sensation or momentary chest tightness during the test (Dicpinigaitis, 2007). If an adverse event is suspected the CI will request a review by the patient's doctor and the doctor will determine if it's safe to continue the study. The CI will complete a Reportable Event on the hospital system.

7. STATISTICAL CONSIDERATIONS

7.1 General Design Issues

The primary hypothesis is that orotracheal intubation inhibits cough response to nebulised citric acid in neurologically intact adults undergoing intubation for elective cardiac surgery.

The CI chose patients undergoing elective cardiothoracic surgery for this study because it provides the opportunity to assess cough reflex before and after intubation. The study will only include patients undergoing coronary artery bypass grafting without valve replacement to obtain some homogeneity in the group. All subjects will be intubated for a minimum of several hours and it is likely that some will be intubated for a number of days. This means data can be collected on subjects with a wide range of intubation times. CRT will be performed before intubation and soon after extubation to measure the effect of intubation on cough reflex.

Repeating the CRT twice per day is practical and will allow the researchers to identify in what 12-hour window most patients recover their cough. This relates to the secondary objective of the study, to determine when, in 12-hour intervals, cough response returns to pre-intubation baseline. Because these data will be used to determine when nurses should screen swallowing, a 12-hour window is sufficient. It is not necessary to know at which hour nurses should screen swallowing, as this is not practical in the ward environment.

The dependent variable for both studies is the response to the cough test. The independent variable is time. Covariates include:

- Complication noted on intubation
- Type of endotracheal tube
- Age
- Gender
- Ethnicity
- Type and amount of anaesthesia used
- Bypass time
- Length of intubation
- Length of stay in ICU
- Time post intubation that CRT1 is tested

7.2 Sample Size and Randomization

The study population is patients undergoing elective cardiothoracic surgery at Wellington Hospital. This is a single cohort observational study. With 100 participants the study will have 90% power to estimate the proportion of patients whose cough reflex has diminished with a measurement error of $\pm 10\%$ (Stata/IC 11.2, StataCorp LP, Texas, USA).

7.3 Data Analyses

The CI will use binomial distribution to estimate the proportion of subjects who do not have a normal cough after intubation.

To meet the secondary aim, time to recovery of cough will be plotted using data points spread across a timeline. These data will be analysed using a Kaplan-Meier Life Table with intervals of twelve hours. Other measures will be analysed using a combination of the McNemar's test, Wilcoxon Sign Rank test, T-Test and the Cox Proportional Hazard Model.

Further analyses will be undertaken on time to recovery of baseline cough, effect of intubation on presence and threshold of cough, correlation between length of intubation and recovery of cough and relationship between other variables and outcome. Specifically the time at which > 50% of patients recover cough response and the time at which > 80% of patients recover cough will be calculated. If a detrimental effect is identified, the CI will also calculate the minimum amount of intubation time that has a significant detrimental effect on cough. Patients who suffered new neurological event will be analysed as a sub-group.

8. DATA COLLECTION AND QUALITY ASSURANCE

All data from screening to CRT results will be recorded on the Case Report Form (Appendix F). All data will be collected by the CI and viewed only by her, the supervisor and co-supervisor. All records will be stored in clearly labeled binder in a locked-filing cabinet and scanned and saved electronically on a password-protected computer/network. Any information taken off site will be identified only by Patient Identification Number and patient initials.

9. PARTICIPANT RIGHTS AND CONFIDENTIALITY

9.1 Ethics Approval

This protocol, the Patient Information Sheet (Appendix B), Consent Form (Appendix C) and any subsequent modifications will be reviewed and approved by the New Zealand Health and Disability Ethics Committee (HDEC) and Canterbury University Human Ethics Committee.

9.2 Informed Consent Forms

Information about the screening process, enrollment and study procedures will be provided verbally and in writing. An interpreter will be made available through Language Line if requested. A signed consent form will be obtained from each participant. A copy will

be given to each participant and this will be documented in the participant's record.

9.3 Participant Confidentiality

All paperwork will be kept in a locked filing cabinet when not in use. Records will also be scanned and saved electronically in a password-protected file. Subjects' names will only appear on the Consent Form (Appendix C) and Record of Participants (Appendix D), which will not leave the site. Other documentation will be identified with the Participant Identification Number (PIN) and participant's initials to maintain confidentiality. All analysis will be completed using the PIN only. Only PIN and initials will identify any information shared with the Co-Investigators. Information will not be released without written permission of the participant, except as necessary for monitoring by the HDEC.

9.4 Study Discontinuation

The HDEC the Canterbury University Ethics Committee, or other government agency may discontinue the study at any time as part of their duties to ensure that research participants are protected

10. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be available for review by the sponsor and the HDEC prior to submission.

11. REFERENCES

Addington, W. R., Stephens, R. E., Widdicombe, J. G., & Rekab, K. (2005). Effect of stroke location on the laryngeal cough reflex and pneumonia risk. *Cough, 1*, 4. doi: 10.1186/1745-9974-1-4

Ajemian, M. S., Nirmul, G. B., Anderson, M. T., Zirlen, D. M., & Kwasnik, E. M. (2001). Routine fiberoptic endoscopic evaluation of swallowing following prolonged intubation: implications for management. *Arch Surg, 136*(4), 434-437.

Barquist, E., Brown, M., Cohn, S., Lundy, D., & Jackowski, J. (2001). Postextubation fiberoptic endoscopic evaluation of swallowing after prolonged endotracheal intubation: A randomized, prospective trial. [Original Article]. *Critical Care Medicine, 29*(9), 1710-1713.

Colice, G. L., Stukel, T. A., & Dain, B. (1989). Laryngeal complications of prolonged intubation. *Chest*, 96(4), 877-884.

Davis, L. A., & Thompson Stanton, S. (2004). Characteristics of dysphagia in elderly patients requiring mechanical ventilation. [Comparative Study]. *Dysphagia*, 19(1), 7-14. doi: 10.1007/s00455-003-0017-7

de Larminat, V., Montravers, P., Dureuil, B., & Desmots, J. M. (1995). Alteration in swallowing reflex after extubation in intensive care unit patients. [Clinical Trial Controlled Clinical Trial]. *Crit Care Med*, 23(3), 486-490.

Dicpinigaitis, P. V. (2007). Experimentally induced cough. [Review]. *Pulm Pharmacol Ther*, 20(4), 319-324. doi: 10.1016/j.pupt.2006.10.003

El Solh, A., Okada, M., Bhat, A., & Pietrantonio, C. (2003). Swallowing disorders post orotracheal intubation in the elderly. [Clinical Trial Comparative Study Controlled Clinical Trial]. *Intensive Care Med*, 29(9), 1451-1455. doi: 10.1007/s00134-003-1870-4

Hogue, C. W., Jr., Lappas, G. D., Creswell, L. L., Ferguson, T. B., Jr., Sample, M., Pugh, D., Lappas, D. G. (1995). SWALLOWING DYSFUNCTION AFTER CARDIAC OPERATIONS: Associated adverse outcomes and risk factors including intraoperative transesophageal echocardiography. *J Thorac Cardiovasc Surg*, 110(2), 517-522.

Leder, S. B., Cohn, S. M., & Moller, B. A. (1998). Fiberoptic endoscopic documentation of the high incidence of aspiration following extubation in critically ill trauma patients. [Research Support, Non-U.S. Gov't]. *Dysphagia*, 13(4), 208-212.

Macht, M., Wimbish, T., Clark, B. J., Benson, A. B., Burnham, E. J., Williams, A., & Moss, M. (2011). Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. [Original Article]. *Critical Care*, 15, 1-9.

Noordally, S. O., Sohawon, S., De Gieter, M., Bellout, H., & Verougstraete, G. (2011). A Study to Determine the Correlation Between Clinical, Fiber-Optic Endoscopic

Evaluation of Swallowing and Videofluoroscopic Evaluations of Swallowing After Prolonged Intubation. [Original Article]. *Nutrition in Clinical Practice*, 26(457-462), 457. doi: 10.1177/0884533611413769

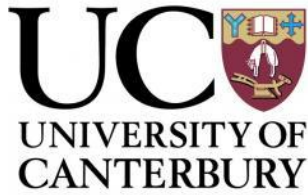
Safdar, N., Dezfulian, C., Collard, H. R., & Saint, S. (2005). Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Review]. *Crit Care Med*, 33(10), 2184-2193.

Tanaka, A., Isono, S., Ishikawa, T., & Nishino, T. (2005). Laryngeal reflex before and after placement of airway interventions: endotracheal tube and laryngeal mask airway. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *Anesthesiology*, 102(1), 20-25.

Wakasugi, Y., Tohara, H., Hattori, F., Motohashi, Y., Nakane, A., Goto, S., . . . Uematsu, H. (2008). Screening test for silent aspiration at the bedside. [Research Support, Non-U.S. Gov't]. *Dysphagia*, 23(4), 364-370. doi: 10.1007/s00455-008-9150-7

12. APPENDICES

- A. Introductory Letter
- B. Patient Information Sheet
- C. Consent Form
- D. Record of Participants
- E. Screening Log
- F. Case Report Form

APPENDIX A – INTRODUCTORY LETTER

Dear Sir or Madam:

You are having heart surgery soon at Wellington Hospital. When you come into hospital, staff will ask if you would like to take part in a research study. This study is looking at the effect of breathing tubes on people's ability to cough. Information from this study will help us provide the best treatment for patients in the future.

Please look at the information provided with this letter to learn more about the study. The information will tell you more about why we are doing the study and what you would be asked to do. When you are admitted staff will ask if you would be willing to meet with the researcher to talk about the study. If you agree, the researcher will visit you to answer any questions you have and see if you fit the criteria for the study. It is up to you if you would like to participate or not. You will receive the same care and medical treatment during your hospital stay whether or not you take part in the study. There will be no direct benefits to you.

Thank you for considering this.

Sincerely,

Dr. Alex Psirides

ICU Consultant

Capital & Coast District Health Board

APPENDIX B - INFORMATION SHEET



INFORMATION

Research Title: A Prospective Study of Cough Response to Nebulised Citric Acid Following Intubation

Primary Researcher:

Molly Kallesen

Department of Speech-Language Therapy

Capital & Coast District Health Board

Department of Communication Disorders, University of Canterbury

(04) 806 2345

Co-Investigators:

Maggie-Lee Huckabee PhD

Senior Lecturer, Department of Communication Disorders, University of Canterbury

Senior Researcher, New Zealand Brain Research Institute

(03) 378 6070

Dr. Alex Psirides

Intensivist

Wellington Intensive Care Unit

Capital & Coast District Health Board

(04) 806 0432

Introduction and aims of the project:

We invite you to take part in a research study. This study is part of a PhD research project with the University of Canterbury. It will measure the effect of a breathing tube on your cough. You have the right to not participate in the study or

stop participating in this study at any time. If you do not participate this will not affect your treatment in any way.

Cough is your body's way of clearing saliva, food or fluid from your airway. Material may get into the lungs and cause an infection if the cough reflex is absent or weak. This could slow recovery after surgery. Sometimes people have trouble swallowing when the breathing tube is removed after surgery. Swallowing problems put people at extra risk of food or fluid entering the lungs, especially if their cough reflex isn't working.

The aim of this project is to measure how the breathing tube affects the cough reflex. We also want to know how long it takes the cough to return to normal after the breathing tube is removed. This information will help the hospital team know who is at the highest risk for getting an infection in the lungs. We can then provide the best and safest treatment.

To test the cough reflex we do something called a Cough Reflex Test (CRT). The CRT involves breathing a mist through a mask. This mist contains citric acid. Citric acid occurs naturally in many things we eat, like oranges, and is used in many packaged foods. When people inhale enough citric acid it makes them cough. Citric acid has been used to cause coughing since the 1950s with no harmful effects. Each cough test takes about ten minutes.

Participant selection:

You are being asked to take part in this study because you are having cardiac surgery. If you agree, we will look at your medical record. We want to know if you have had a neurological disorder, head or neck cancer, swallowing problems or damage to your throat. If not, you will be enrolled in the study and have the cough test. The study will include a total of 100 people who are having cardiac surgery. Remember, you can withdraw from the study at any time.

The research procedure:

This is what will happen if you agree to take part in this study:

1. Once you have agreed to take part in the study, the researcher will look at your medical records and ask you a few questions to make sure you can participate.
2. Then the researcher will place a small amount of liquid into a nebuliser. The nebuliser is a device that turns the liquid into mist so you can inhale it. You will be asked to breathe the mist in for 15 seconds.
3. The mist you inhale may make you feel like coughing. You will be asked to try not to cough.
4. After 15 seconds the mask will be taken off and you can relax. The test will be repeated up to four more times.
5. If you *do not* cough on at least two of these tests they will be repeated with a different solution.
6. If you *do not* cough on *any* of the tests you will be finished with the study.
7. If you *do* cough on two of the three tests you will continue with the study (Step 8 and 9).
8. After your surgery, the test will be repeated in the same way within two hours of the breathing tube being removed. This usually happens within about twelve hours of your surgery, but it may be later.
9. The test will be repeated each morning and evening until your cough returns to normal. This may happen immediately or take several days.

Outcome Measurements:

We will measure if your cough is present or absent after the removal of the breathing tube. If your cough reflex is absent, we will determine how long it takes for it to return to normal by repeating the test. We will also record things about your surgery, including the type of surgery you had and what medicines you were given.

Risks and Benefits:

There will be no direct benefit to you if you take part in this study. There have been no harmful effects from the cough test in other research. You may feel slightly tight in your chest when inhaling the mist. Coughing may feel uncomfortable after surgery, but coughing is important to your recovery and the doctors and nurses will encourage you to cough. A trained person will monitor you carefully during the cough test. We hope that the results of this study will help us to make better decisions about how we treat people after they have been intubated.

Participation:

If you do agree to take part in this study you are free to stop at any time. You do not need to give a reason for stopping. Your family or whānau can also withdraw on your behalf. Stopping will not change the care you receive. Your participation in the study will be stopped should any harmful effects appear.

Confidentiality:

The results of this study may be presented at meetings in New Zealand and in other countries. They may also be printed in medical journals. No information that could identify you will be used in any reports. This form and other paperwork will be locked in a filing cabinet in the Speech-Language Therapy department at the hospital or will be stored on password-protected computers. All records will be stored for a period of ten years then sent to the national archive. Results from this study may be used in future studies that have ethical approval from the New Zealand Health and Disability Ethics Committee.

Results:

You can have copies of the publications that arise from this research. You can also choose to have someone discuss the results of the study with you. It will be several months after the study is completed before any information is available. Please let the Primary Researcher know if you would like her to share the results with you.

Questions:

You may have a friend, family, or whanau support person to help you understand the risks and benefits of this study. They are welcome to speak to the Primary Researcher with your permission.

Please contact the Primary Researcher listed on the front page of this information sheet if you have any questions.

An interpreter can be provided if you need one.

This project has been reviewed and approved by the University of Canterbury Human Ethics Committee (Private Bag 4800, Christchurch, email human-ethics@canterbury.ac.nz).

You can contact a Health and Disability Advocate if you have any questions or concerns about your rights:

Wellington Office: (04) 389 2502

National Free Phone: 0800 555 050

Free Fax: 0800 2 SUPPORT or 0800 2787 7678

Email: advocacy@hdc.org.nz

APPENDIX C – CONSENT FORM



Cough reflex testing after intubation

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

I, _____, have read and I understand the Information Sheet Version 2.0 for volunteers taking part in the study designed to collect information about the usefulness of cough reflex testing. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had this project explained to me by Molly Kallesen, the main researcher.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my current, continuing or future health care. My family or whānau can also withdraw on my behalf. I understand that if I choose to withdraw from the study, I may also withdraw all information that I have provided.

I understand that the information obtained from this research may be published. However, I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

Cough Reflex Testing

I understand that the investigation will be stopped if it should appear harmful to me and I know who to contact if I have any side effects to the study or have any questions about the study.

I understand the potential risks of participation in the study as explained to me by the researcher.

I understand that I do not receive payment for this study.

I have had time to consider whether to take part.

I wish to receive a copy of the results.

YES / NO

I, _____ hereby consent to take part in this study.

Date _____

Signature _____

Signature of researcher _____ Name of researcher: Molly Kallesen

Name of primary researcher and contact phone numbers:

Name: Molly Kallesen at Capital & Coast District Health Board
04 806 2345 or molly.kallesen@ccdhb.org.nz

(Note: A copy of the consent form to be retained by participant and (in the case of patients) a copy to be placed in the medical file.)

APPENDIX E – SCREENING LOG

[illegible]

APPENDIX F – CASE REPORT FORM

Patient Sticky

Patient Identification Number :

Date of screening and enrolment:

Date of completion of study:

Patient Initials:		
Patient Identification Number:		
Date of Birth:		
Age:		
Gender:		
Ethnicity:		
Patient Questions:		
“Have you ever had difficulty swallowing?”	Yes	No
If yes: - “Please describe the difficulty.” - “Have you had any tests done for it?” - “When did it start?” - “Is it still a problem?”	Comments:	
Baseline Characteristics:		
History of Dysphagia	Yes	No
History of Head & Neck Cancer	Yes	No
History of neurological disorder (e.g., stroke, Parkinson’s, MS, TBI)	Yes	No
Able to provide consent	Yes	No

Comments on above:	
List of medications at the time of hospital admission	
Patient Initials:	
Patient Identification Number:	
Any medications started in hospital	
Any medications withheld prior to surgery and number of days they were withheld	
Medications given as pre-med and dose	

COUGH REFLEX TEST 1 (BASELINE):			
Record for each trial A = absent, P = present, X = not administered			
Date of CRT			
Time of CRT			
Concentration	Presentation 1	Presentation 2	Presentation 3
____ mol / saline			
____ mol / saline			
____ mol / saline			
____ mol / saline			
Subject Threshold = _____ OR Absent Cough (Discontinue)			
Adverse events: NO YES (See adverse event record)			
Comments:			

Patient Initials:		
Patient Identification Number:		
OPERATIVE DATA:		
Operation performed (APACHE III Subcode for Cardiac Surgery)		
Time of induction		
Surgeon:		
Anaesthetist:		
Perfusionist:		
Time of knife to skin		
Time onto bypass		
Time of cross clamp removal		
Total bypass time		
Cross clamp time		
IABP (balloon pump) used	Yes	No
Intervention successfully applied	Yes	No
Type and size of endotracheal tube		
Complications noted during intubation	Yes	No
Any indication of RLN damage?	Yes	No
Comments		

Patient Initials:		
Patient Identification Number:		
Induction		
Midazolam dose (mg)		
Fentanyl dose (mcg)		
Analgesia		
Total supplemental fentanyl (mcg)		
Morphine dose (mg)		
Euroscore		
Other drugs		
Were any non-protocol drugs administered during cardiac anaesthesia?	Yes	No
If yes, give drug(s), dose(s) and reason for administration of non-protocol drug		
Length of stay		
ICU admission date and time		
ICU discharge time		
Hospital discharge date		

Patient Initials:			
Patient Identification Number:			
COUGH REFLEX TEST 2 (POST EXTUBATION):			
Record for each trial A = absent, P = present, X = not administered			
Date of extubation			
Time of extubation			
Date of CRT			
Time of CRT			
Begin at subject's baseline threshold =			
Concentration	Presentation 1	Presentation 2	Presentation 3
____ mol / saline			
____ mol / saline			
____ mol / saline			
____ mol / saline			
Subject Threshold = _____ OR Absent Cough			
Adverse events: NO YES (See adverse event record)			
Patient Completed Study OR Follow Up OR Discontinue			
Comments:			

Patient Initials:			
Patient Identification Number:			
COUGH REFLEX TEST # ____			
Record for each trial A = absent, P = present, X = not administered			
Date of CRT		Time of CRT	
Begin at subject's baseline threshold =			
Concentration	Presentation 1	Presentation 2	Presentation 3
x.x mol			
x.x mol			
x.x mol			
Subject Threshold = _____ OR Absent Cough			
Adverse events: NO YES (See adverse event record)			
Patient Completed Study OR Follow Up OR Discontinue			
Comments:			

Testing Cough Reflex after Extubation on the Intensive Care Unit: A Validation Study

Co-ordinating Investigator:

**Molly Kallesen, Speech-Language Therapist, PhD Candidate,
University of Canterbury**

Supported by:

**University of Canterbury and The New Zealand Brain Research
Institute**

STUDY TEAM ROSTER

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(64) 4 806 0432

PRÉCIS

Study Title

Testing Cough Reflex after Extubation on the Intensive Care Unit: A validation study.

Objectives

The primary objective is to determine the sensitivity and specificity of nebulized citric acid for detecting the presence of cough reflex on aspiration by analyzing the correlation between response to cough reflex testing (CRT) and presentation of airway compromise on endoscopy.

The secondary objective is to determine the sensitivity and specificity of detecting silent aspiration when aspiration is observed on videoendoscopy (VES).

Participants

108 Intensive Care Unit (ICU) patients who meet the inclusion criteria. Enrollment will be capped at a maximum of 54 participants with a primary surgical diagnosis and 54 with a non-surgical primary diagnosis. Participants will be enrolled consecutively, seven days a week, two weeks on and one week off.

Method

The CI will consider all ICU patients who meet the inclusion criteria after extubation to enroll in the study. The CI will visit ICU each morning and evening as described in the Study Enrollment Procedures section below and liaise with the Associate Charge Nurse Manager to identify potential participants who have been extubated in the previous 24 hours. Participants who consent and who are not excluded will undergo a CRT followed within one hour by a VES, both performed by the CI. The CI will judge the cough to be present or absent and if present, as weak or strong. The VES will be recorded by the CI and rated later by a SLT blinded to results of CRT. The blinded SLT will rate aspiration as absent, present or trace and for those with present or trace aspiration, rate cough as present or absent.

Outcome measures.

Dependent variable:

- Cough to aspiration, rated as present or absent

Independent variable:

- Response to cough reflex test, classified as present or absent and if present

Covariates:

- Time from extubation
- Length of intubation
- Age
- Gender
- Ethnicity
- Diagnosis Group (Surgical or Non-surgical)
- APACHE III score
- Opiate dose in the previous 24 hours
- Secretion rating score (Murray et al., 1996)

Analysis will primarily address the sensitivity and specificity of CRT to predict cough to aspiration on VES.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to determine the sensitivity and specificity of nebulized citric acid for detecting the presence of cough reflex on aspiration by analyzing the correlation between response to cough reflex testing (CRT) and presentation of airway compromise on endoscopy.

1.2 Secondary Objectives

The secondary objective is to determine the prevalence of silent aspiration in this population

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Each year in Capital & Coast ICU approximately 1200 patients are intubated. Dysphagia, or disordered swallowing, is common post-intubation with studies in the general ICU population indicating that over 50% of patients have some level of dysphagia soon after extubation. Up to one half of these patients aspirate “silently” or without overt evidence of aspiration, such as coughing. Patients who aspirate silently are particularly difficult to detect as ICU staff use the presence of coughing with food and drink to determine if patients have dysphagia. Currently, patients are only referred to speech-language therapy for a swallowing assessment if they demonstrate overt signs of aspiration and it is likely that many patients are allowed to eat and drink while silently aspirating. Aspiration can be a causal factor in the development of pneumonia, which is the most common nosocomial infection in ICU. Development of pneumonia significantly increases length of stay, risk of death and cost of treatment (Safdar et al., 2005).

2.2 Study Rationale

Dysphagia and aspiration after orotracheal intubation in the Intensive Care Unit (ICU) population is common (Ajemian et al., 2001; de Larminat et al., 1995; El Solh et al., 2003; Macht et al., 2011; Noordally et al., 2011). Studies measuring frequency of aspiration in a general ICU population post-extubation indicate that it occurs in 27% to 56% of patients (Ajeman, El Solh, Noordally). Intensive care patients who aspirate are at increased risk of developing pneumonia. Pneumonia results in increased length of stay, mortality and cost of care (Safdar et al., 2005).

Recently extubated ICU patients are particularly at risk for silent aspiration, or aspiration without spontaneous cough. Most studies that have looked specifically at silent aspiration as diagnosed on instrumental assessment report silent aspirators as a percentage of total aspirators, with rates ranging from 22% to 44% (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al., 1995; Leder et al., 1998). However silent aspiration cannot be reliably identified by bedside clinical assessment (Barquist et al., 2001; Davis & Thompson Stanton, 2004; El Solh et al., 2003; Hogue et al.,

1995; Leder et al., 1998). Often these patients are allowed to eat and drink soon after extubation, potentially putting them at increased risk of aspirating.

Sensory testing of patients after orotracheal intubation suggests that airway reflexes are impaired in these patients in the short and medium term (Colice et al., 1989; Tanaka et al., 2005). Airway sensation in the recently extubated population has been tested by injection of water into the glottis (Tanaka et al., 2005), presence of a gag on laryngoscopy (Colice et al., 1989), and light touch to the aryepiglottic folds using a laryngoscope (Scheel et al., 2009).

The Cough Reflex Test (CRT) is emerging as a useful tool for testing subjects' ability to protect their airway through reflexive cough (Addington et al., 2005; Wakasugi et al., 2008). Currently, there is no evidence in the literature describing the use of CRT to test sensation after extubation. Most research relating cough reflex to safety during swallowing has been in the stroke population. Absent cough to CRT with acidic tussives (i.e. citric acid and tartaric acid) has high specificity as a predictor of aspiration pneumonia (Addington et al., 2005; Wakasugi et al., 2008). In 2005, Addington and colleagues reported on 818 consecutive stroke patients who all underwent CRT with tartaric acid before starting oral intake after acute stroke. Patients who failed the CRT were kept nil by mouth. Three and one half percent of subjects with a normal response to CRT developed pneumonia during their hospital stay compared to 10% of subjects with a weak response to CRT and 16% of patients with an absent cough response (Addington et al., 2005). Research recently conducted in New Zealand by the supervisor of this project, Dr. Maggie-Lee Huckabee, Anna Miles and their colleagues (Miles, Moore, et al., 2013) showed a significant relationship between CRT result and response to aspiration on instrumental assessment. CRT with nebulized citric acid is gaining traction as a tool for dysphagia assessment in New Zealand, particularly with stroke patients.

To determine sensitivity and specificity, CRT is compared to a "gold standard" assessment. The two methods of instrumental assessment of dysphagia used by speech-language therapists are Videofluoroscopic Swallowing Studies (VFSS) and VES. For this study we are using VES because it offers many advantages in the ICU environment. It can be performed at bedside, requires fewer resources than VFSS and is good for assessing response to aspiration (Ref). Miles et.al. has already looked at validity of CRT in a general ward environment with primarily stroke patients (Miles, Moore, et al., 2013). However, in recently extubated ICU patients the etiology of dysphagia is different and it will be worth ensuring

that the CRT is valid with this population, rather than assuming that the results of general ward patients applies.

Given that aspiration places ICU patients at risk of pneumonia, silent aspiration is common in patients after orotracheal intubation and CRT testing is a useful tool for determining risk of silent aspiration, it follows that it may be useful to use CRT with patients after orotracheal intubation to help determine safety of oral intake. However, we do not currently know if CRT is a sensitive and specific indicator of silent aspiration in the intubated population. This research study will test the hypothesis that recently intubated ICU patients with an absent cough to CRT will demonstrate greater incidence of silent aspiration during VES and people with a strong cough will demonstrate lower incidence of silent aspiration during VES.

3. STUDY DESIGN

This is a prospective cohort observational study.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria below to participate in this study.

- Extubated within the 24 hours preceding enrollment
- Have been an inpatient on the Intensive Care Unit at the time of extubation
- 18 years of age or older
- Be a candidate for oral intake (e.g., not nil by mouth for recent gastric surgery)
- Enrollment will be capped at 54 participants with a primary surgical requirement for intubation (e.g., post cardiothoracic surgery) and 54 with a non-surgical reason for intubation (e.g., pneumonia, stroke)

4.2 Exclusion Criteria

Participants meeting any of the exclusion criteria at baseline will be excluded from study participation.

- Inability or unwillingness of individual or relative/whanau/friend to give consent.
- Glasgow Coma Scale score less than 13
- Recent cannulation (tracheostomy)
- Have a history of severe (life threatening) nosebleeds
- Have recent (less than four weeks) facial or base of skull fractures
- Be for palliative treatment

4.3 Study Enrollment Procedures

- Patients will be enrolled Monday through Sunday, 14 days on and seven days off. This is to ensure the study is practical to complete for a single researcher. Enrollment is expected to take three months.
- The ICU nurse will provide the relative/whanau member/friend of the patient with an Information Sheet for Relative/Whanau Member/Friend (Appendix A) during the period of intubation. The patient will also receive a Participant Information Sheet (Appendix B) at the time of extubation.
- When a patient is extubated, nursing staff will ask the patient and relative/whanau member/friend (if present) if they would be willing to meet with the researcher.
- Each morning and evening of the enrollment period, the CI will round the unit and ask nurses if they have any potential participants who have agreed to meet the CI.
- The CI will provide further verbal information and the potential participant or relative/whanau member/friend will have the opportunity to discuss the study.
- If there is any question about the patient's competence to consent, and in all cases where the patient's GCS is less than fifteen, the CI will ask the treating doctor if the patient is competent.
- Consenting participants will sign the Participant Consent Form (Appendix B). Relative/whanau/friends will sign the Consent Form for Relative/Whanau/Friend (Appendix A). All participants will be recorded in the Record of Participants (Appendix C).
- When the quota has been reached for a diagnostic group (Surgical or Non-surgical) enrollment for that group will stop but enrollment for the other group will continue.
- Patients who do not consent or who are excluded from the study will be recorded in the Screening Log (Appendix D).

5. SCHEDULE OF EVALUATIONS

5.1 Cough Reflex Test

Once a subject is enrolled, the CI will perform a Cough Reflex Test (CRT). The procedure for CRT will be the same each time and is described below.

- The patient must be sitting up in a bed or chair for assessment with head raised at least 60 degrees.
- Up to three concentrations of citric acid will be trialed. These are 0.4, 0.6 and 0.8 mol (diluted in .9% sodium chloride).
- The CI will first test with the lowest concentration of citric acid.
- At least 2.5 milliliters of sterile citric acid solution will be placed in a nebulizer cup, which is attached by tubing to a DeVilbiss Pulmomate nebulizer with a free-flow rate of eight liters per minute.
- A facemask will be attached by connecting tubing to the nebulizer. The CI will place the facemask over the subject's nose and mouth and ask them to quietly breath for 15 seconds. The subject will be told that they should try not to cough.
- There will be a break of at least one minute between each trial.
- If the subject does cough at least twice on two of three trials the cough will be judged present.
- If the cough is absent, the CI will repeat the CRT with the next higher concentration, continuing until the patient achieved a present strong cough or until the CI determines that the participant has an absent cough on all concentrations.
- The citric acid trials will be interspersed with placebo trials of normal saline water. If the patient coughs on two trials of normal saline, the cough will be considered abnormal and the patient will be excluded from the study.
- If the subject's cough is present on the first concentration of citric acid and absent on at least one of the saline solution tests, the test is complete.
- Results will be recorded on the Case Report Form (Appendix E) and saved with the study records.

5.2 Videoendoscopic Evaluation of Swallowing (VES)

The CI will perform the VES within one hour of the CRT. The procedure for VES is described below.

- Participant is seated upright at least 45° in a bed or chair
- CI applies lubricant to endoscope.
- CI guides endoscope along floor of nose.
- CI then guides endoscope into nasopharynx and positions endoscope for an optimal view of larynx.
- An assisting nurse or clinician will then provide participant with 5 controlled single sips of thin fluid. If the participant manages this without significant aspiration, the nurse will next provide 150 mls to be taken via rapid ingestion.
- The study will be recorded for review by an SLT blinded to the results of CRT. Recordings will be identified by study name and PIN.
- Any significant findings that represent a potential risk to the participant, such as aspiration, absence of cough, poor control of secretions or laryngeal pathology will be recorded in the medical record and may be discussed with treating clinicians with the participant's permission (as covered in Consent Form)
- Tasks will be recorded on the Case Report Form.
- The FEES will be recorded electronically, identified by PIN only and sent via encoded zip files to the reviewer. The reviewer will complete the VES Rating Form (Appendix H). If aspiration occurs on any trial aspiration will be recorded as present.

6. SAFETY ASSESSMENTS/ADVERSE EVENTS

An adverse event is defined as any unfavorable and unintended diagnosis, symptom, sign syndrome or disease that is not related to the subject's medical condition. The CI does not anticipate adverse events. Subjects may experience a choking sensation or momentary chest tightness during the CRT (Dicpinigaitis, 2007). In a study of outpatients undergoing VES, most found it not uncomfortable or mildly uncomfortable (62%), while 32% found it moderately uncomfortable (Cohen et al., 2003). In rare cases patients can have minor, self-limiting nosebleeds or fainting (Warnecke et al., 2009). If an adverse event is suspected the CI will request a review by the patient's doctor and the doctor will determine if it's safe to continue the study. The CI will complete a Reportable Event on the hospital system and report to ethics committee.

7. STATISTICAL CONSIDERATIONS

7.1 General Design Issues

CRT as a screening test is being compared to the gold standard of VES. Analysis will aim to determine the sensitivity and specificity of CRT to predict absence of cough to aspiration on VES.

The CI chose a general ICU population so that sample group is representative of a broad spectrum of patients and so that the results can be applied to a general ICU population. Because there is a predominance of surgical patients admitted to ICU, the enrollment is capped at 54 surgical patients and 54 non-surgical patients. This is to ensure adequate numbers of participants in each group for analysis.

The CI is performing both the CRT and VES, which introduce bias. It is not practical to have different clinicians perform each test due the timing – both examinations need to be done within one hour and within 24 hours of extubation. This is prohibitive because of cost and resourcing. The design controls for bias by the order of the examinations and using an SLT blinded to the results of the CRT to interpret the VES. The CRT will be performed first and the CI will not have an expectation of performance. The results of the CI will be recorded prior to the VES. The VES will be performed by the CI, recorded, and sent to a blinded SLT for interpretation. The blinded SLT will be indicating if aspiration is present or absent and if present, if cough was present or absent.

7.2 Sample Size

Using Method 2 of Jialiang Li and Jason Fine’s suggested methods for sample size and power calculations for disease screening tests (Li & Fine, 2004), with a “no cough” prevalence of 0.3 (30%) or less, 108 people will give us 80% power to detect a reduction of sensitivity from 90% to 60% at the .05 level of significance.

7.3 Data Analyses

The CI will calculate the proportion of participants with aspiration and silent on VES post intubation. These data will then be used to compare to the results of the cough test to calculate sensitivity and specificity with 95% confidence intervals of the CRT to predict presence or absence of cough to aspiration on VES. This will be repeated for each

concentration of citric acid. In addition, the CI will perform stratified Chi-squared test to test for the significance of a relationship between the covariates and presence or absence of aspiration post-intubation ($p < .05$). The cohort will be analysed as a whole and by diagnostic subgroup (surgical versus non-surgical).

8. DATA COLLECTION AND QUALITY ASSURANCE

All data from screening to CRT results will be recorded on the Case Report Form. All data will be collected by the CI and viewed only by her, her supervisor and co-supervisor. All records will be stored in clearly labeled binder in a locked-filing cabinet and scanned and saved electronically on a password-protected computer/network. Any information taken off site will be identified only by Patient Identification Number and patient initials.

9. PARTICIPANT RIGHTS AND CONFIDENTIALITY

9.1 Ethics Approval

This protocol, the information sheets, consent forms and any subsequent modifications will be reviewed and approved by the New Zealand Health and Disability Ethics Committee (HDEC) and Canterbury University Human Ethics Committee.

9.2 Informed Consent Forms

Information about the screening process, enrollment and study procedures will be provided verbally and in writing. A signed consent form will be obtained from each participant. When a participant is not competent to consent (as determined by treating doctor) the CI will provide written and verbal information to an appropriate relative/whanau/friend of the participant and ask them to sign the Statement for Relative/Whanau/Friend if they agree. A copy of the consent form/statement will be given to each participant and this will be documented in the participant's record.

If a participant is not competent at the time of the study but regains competence during the course of their hospital stay, the CI will visit the participant, fully explain the study, and seek their consent. The CI will explain that the participant has the option of withdrawing their information from the study.

9.3 Participant Confidentiality

All paperwork will be kept in a locked cupboard when not in use. Records will also be scanned and saved electronically on a password-protected computer. Participants' names will only appear on the Consent Form, Record of Participants, and Screening Log, which will not leave the site. Other documentation will be identified with the Participant Identification Number (PIN) and participant's initials only to maintain confidentiality. All analysis will be completed using the PIN only. Only PIN and initials will identify any information shared with the Co-Investigators. Information will not be released without written permission of the participant, except as necessary for monitoring by the HDEC.

9.4 Study Discontinuation

All data will be collected unless an unexpected complication arises and the researcher feels the study may be creating risks for participants. The study may also be discontinued if midway analysis demonstrates that results are reached sooner than anticipated.

10. PUBLICATION OF RESEARCH FINDINGS

The results will be summarized and submitted to an international, peer-reviewed journal for publishing.

11. REFERENCES

- Addington, W. R., Stephens, R. E., Gilliland, K., & Rodriguez, M. (1999). Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke. *Arch Phys Med Rehabil*, 80(2), 150-154.
- Addington, W. R., Stephens, R. E., & Gilliland, K. A. (1999). Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke: an interhospital comparison. *Stroke*, 30(6), 1203-1207.

- Addington, W. R., Stephens, R. E., Ockey, R., Kann, D., & Rodriguez, M. (1995). A New Aspiration Screening Test to Assess the Need for Modified Barium Swallow Study - Addington. *Arch Phys Med Rehabil*, 76, 1040.
- Addington, W. R., Stephens, R. E., Widdicombe, J. G., & Rekab, K. (2005). Effect of stroke location on the laryngeal cough reflex and pneumonia risk. *Cough*, 1, 4. doi:10.1186/1745-9974-1-4
- Aderinto - Adike, A. O., & Quigley, E. M. (2014). Gastrointestinal motility problems in critical care: a clinical perspective. *Journal of digestive diseases*, 15(7), 335-344.
- Ajemian, M. S., Nirmul, G. B., Anderson, M. T., Zirlen, D. M., & Kwasnik, E. M. (2001). Routine fiberoptic endoscopic evaluation of swallowing following prolonged intubation: implications for management. *Arch Surg*, 136(4), 434-437.
- Amri, M., & Car, A. (1988). Projections from the medullary swallowing center to the hypoglossal motor nucleus: A neuroanatomical and electrophysiological study in sheep. *Brain Res*, 441(1-2), 119-126.
- Ando, A., Farrell, M. J., & Mazzone, S. B. (2014). Cough-related neural processing in the brain: a roadmap for cough dysfunction? *Neuroscience & Biobehavioral Reviews*, 47, 457-468.
- Apostolakis, E., Papakonstantinou, N. A., Baikoussis, N. G., & Papadopoulos, G. (2015). Intensive care unit-related generalized neuromuscular weakness due to critical illness polyneuropathy/myopathy in critically ill patients. *Journal of anesthesia*, 29(1), 112-121.
- Apostolopoulou, E., Bakakos, P., Katostaras, T., & Gregorakos, L. (2003). Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. *REspiratory Care*, 48(7), 681-688.

- Armstrong, W. B., & Netterville, J. L. (1995). Anatomy of the larynx, trachea, and bronch. *Otolaryngol Clin North Am*, 28(4), 685.
- Aviv, J. E. (2000). Prospective, randomized outcome study of endoscopy versus modified barium swallow in patients with dysphagia. *Laryngoscope*, 110(4), 563-574.
- Aviv, J. E., Kim, T., Sacco, R. L., Kaplan, S., Goodhart, K., Diamond, B., & Close, L. G. (1998). FEESST: a new bedside endoscopic test of the motor and sensory components of swallowing. *Ann Otol Rhinol Laryngol*, 107(5 Pt 1), 378-387.
- Badr, C., Elkins, M. R., & Ellis, E. R. (2002). The effect of body position on maximal expiratory pressure and flow. *Australian Journal of Physiotherapy*, 48(2), 95-102.
- Barker, J., Martino, R., Reichardt, B., Hickey, E. J., & Ralph-Edwards, A. (2009). Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. *Can J Surg*, 52(2), 119-124.
- Barquist, E., Brown, M., Cohn, S., Lundy, D., & Jackowski, J. (2001). Postextubation fiberoptic endoscopic evaluation of swallowing after prolonged endotracheal intubation: A randomized, prospective trial. *Critical Care Medicine*, 29(9), 1710-1713.
- Barros, M. J., Zammattio, S. J., & Rees, P. J. (1990). Importance of inspiratory flow rate in the cough response to citric acid inhalation in normal subjects. *Clinical Science*, 78(5), 521-525.
- Bastian, R. W., & Riggs, L. C. (1999). Role of sensation in swallowing function. *Laryngoscope*, 109(12), 1974-1977.
- Baumgartner, C. A., Bewyer, E., & Bruner, D. (2008). Management of Communication and Swallowing in Intensive Care. *AACN Advanced Critical Care*, 19(4), 433-443.
- Becklake, M. R., & Kauffmann, F. (1999). Gender differences in airway behaviour over the human life span. *Thorax*, 54(12), 1119-1138.

- Bhattacharyya, N. (2014). The prevalence of dysphagia among adults in the United States. *Otolaryngology--Head and Neck Surgery*, 151(5), 765-769.
- Bickerman, H. A., & Barach, A. L. (1954). The experimental production of cough in human subjects induced by citric acid aerosols; preliminary studies on the evaluation of antitussive agents. *Am J Med Sci*, 228(2), 156-163.
- Bickerman, H. A., German, E., Cohen, B. M., & Itkin, S. E. (1957). The cough response of healthy human subjects stimulated by citric acid aerosol. II. Evaluation of antitussive agents. *Am J Med Sci*, 234(2), 191-206.
- Bishop, M. J., Hibbard, A. J., Fink, B. R., Vogel, A. M., & Weymuller, E. A., Jr. (1985). Laryngeal injury in a dog model of prolonged endotracheal intubation. *Anesthesiology*, 62(6), 770-773.
- Bordon, A., Bokhari, R., Sperry, J., Testa, D. t., Feinstein, A., & Ghaemmaghami, V. (2011). Swallowing dysfunction after prolonged intubation: analysis of risk factors in trauma patients. *Am J Surg*, 202(6), 679-682; discussion 682-673. doi:10.1016/j.amjsurg.2011.06.030
- Bouza, E., Pérez, A., Muñoz, P., Pérez, M. J., Rincón, C., Sánchez, C., . . . Riesgo, M. (2003). Ventilator-associated pneumonia after heart surgery: a prospective analysis and the value of surveillance. *Critical Care Medicine*, 31, 1964-1970.
- Bouza, E., Pérez, M. J., Munoz, P., Rincón, C., Barrio, J. M., & Hortal, J. (2008). Continuous aspiration of subglottic secretions in the prevention of ventilator-associated pneumonia in the postoperative period of major heart surgery. *Chest*, 135(5), 938-946.
- Brooks, S. M. (2011). Perspective on the human cough reflex. *Cough*, 7, 10. doi:10.1186/1745-9974-7-10

- Brown, C. V., Hejl, K., Mandaville, A. D., Chaney, P. E., Stevenson, G., & Smith, C. (2011). Swallowing dysfunction after mechanical ventilation in trauma patients. *J Crit Care*, 26(1), 108 e109-113. doi:10.1016/j.jcrc.2010.05.036
- Burgess, G. E., 3rd, Cooper, J. R., Jr., Marino, R. J., Peuler, M. J., & Warriner, R. A., 3rd. (1979). Laryngeal competence after tracheal extubation. *Anesthesiology*, 51(1), 73-77.
- Canning, B. J. (2006). Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. *Chest*, 129(1 Suppl), 33S-47S. doi:10.1378/chest.129.1_suppl.33S
- Canning, B. J., Mazzone, S. B., Meeker, S. N., Mori, N., Reynolds, S. M., & Undem, B. J. (2004). Identification of the tracheal and laryngeal afferent neurones mediating cough in anaesthetized guinea-pigs. *J Physiol*, 557(Pt 2), 543-558. doi:10.1113/jphysiol.2003.057885
- Canning, B. J., & Mori, N. (2011). Encoding of the cough reflex in anesthetized guinea pigs. *Am J Physiol Regul Integr Comp Physiol*, 300(2), R369-377. doi:10.1152/ajpregu.00044.2010
- Carnaby-Mann, G., & Lenius, K. (2008). The bedside examination in dysphagia. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 747-768.
- Chang, A. B., & Widdicombe, J. G. (2007). Cough throughout life: children, adults and the senile. *Pulm Pharmacol Ther*, 20(4), 371-382.
- Chevret, S., Hemmer, M., Carlet, J., & Langer, M. (1993). Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. *Intensive Care Med*, 19(5), 256-264.
- Chung, K., & Chang, A. (2002). Therapy for cough: active agents. *Pulm Pharmacol Ther*, 15(3), 335-338.

- Cichero, J. A., Heaton, S., & Bassett, L. (2009). Triaging dysphagia: nurse screening for dysphagia in an acute hospital. *Journal of clinical nursing*, 18(11), 1649-1659.
- Cohen, M. A., Setzen, M., Perlman, P. W., Ditkoff, M., Mattucci, K. F., & Guss, J. (2003). The Safety of Flexible Endoscopic Evaluation of Swallowing With Sensory Testing in an Outpatient Otolaryngology Setting. *Laryngoscope*, 113(1), 21-24. doi:10.1097/00005537-200301000-00004
- Colice, G. L. (1992). Resolution of laryngeal injury following translaryngeal intubation. *Am Rev Respir Dis*, 145(2 Pt 1), 361-364.
- Colice, G. L., Stukel, T. A., & Dain, B. (1989). Laryngeal complications of prolonged intubation. *Chest*, 96(4), 877-884.
- Colodny, N. (2002). Interjudge and intrajudge reliabilities in fiberoptic endoscopic evaluation of swallowing (fees) using the penetration-aspiration scale: a replication study. *Dysphagia*, 17(4), 308-315. doi:10.1007/s00455-002-0073-4
- Colton House, J., Noordzij, J. P., Murgia, B., & Langmore, S. (2011). Laryngeal injury from prolonged intubation: a prospective analysis of contributing factors. *Laryngoscope*, 121(3), 596-600. doi:10.1002/lary.21403
- Cosgrove, J. F., & Carrie, S. (2015). Indications for and management of tracheostomies. *Surgery (Oxford)*, 33(4), 172-179.
- Daly, E., Miles, A. C., Scott, S., & Gillham, M. (2016). Finding the red flags: Swallowing difficulties after cardiac surgery in patients with prolonged intubation. *J Crit Care*, 31(1), 119-124.
- Daniels, S. K., Anderson, J. A., & Willson, P. C. (2012). Valid Items for Screening Dysphagia Risk in Patients With Stroke A Systematic Review. *Stroke*, 43(3), 892-897.
- Daniels, S. K., & Huckabee, M.-L. (2014). Dysphagia Following Stroke. 376.

- Davenport, Sapienza, C., & Bolser, D. (2002). Psychophysical assessment of the urge-to-cough. *European Respiratory Review*, 12(85), 249-253.
- Davenport, Vovk, A., Duke, R. K., Bolser, D. C., & Robertson, E. (2009). The urge-to-cough and cough motor response modulation by the central effects of nicotine. *Pulm Pharmacol Ther*, 22(2), 82-89.
- Davies, S. E. (2016). Predicting and preventing aspiration pneumonia in patients with acute stroke and dysphagia.
- Davis, L. A., & Thompson Stanton, S. (2004). Characteristics of dysphagia in elderly patients requiring mechanical ventilation. *Dysphagia*, 19(1), 7-14. doi:10.1007/s00455-003-0017-7
- de Camargo, F. P., Ono, J., Park, M., Caruso, P., & Carvalho, C. R. R. (2010). An evaluation of respiration and swallowing interaction after orotracheal intubation. *Clinics*, 65(9), 919-922. doi:10.1590/S1807-59322010000900015
- De Jonghe, B., Bastuji-Garin, S., Durand, M.-C., Malissin, I., Rodrigues, P., Cerf, C., . . . Sharshar, T. (2007). Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Critical Care Medicine*, 35(9).
- de Larminat, V., Montravers, P., Dureuil, B., & Desmonts, J. M. (1995). Alteration in swallowing reflex after extubation in intensive care unit patients. *Crit Care Med*, 23(3), 486-490.
- DeVita, M. A., & Spierer-Rundback, L. (1990). Swallowing disorders in patients with prolonged orotracheal intubation or tracheostomy tubes. *Crit Care Med*, 18(12), 1328-1330.
- Devlin, J. W., and Russel J. Roberts. (2009). Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. *Critical Care Clinics*, 25(3), 431-449.

- Dicpinigaitis. (2003). Cough reflex sensitivity in cigarette smokers. *Chest*, 123(3), 685-688.
- Dicpinigaitis. (2007). Experimentally induced cough. *Pulm Pharmacol Ther*, 20(4), 319-324.
doi:10.1016/j.pupt.2006.10.003
- Dicpinigaitis, Chang, A. L., Dicpinigaitis, A. J., & Negassa, A. (2016). Effect of e-Cigarette Use on Cough Reflex Sensitivity. *CHEST Journal*, 149(1), 161-165.
- Dicpinigaitis, & Rauf, K. (1998). The influence of gender on cough reflex sensitivity. *CHEST Journal*, 113(5), 1319-1321.
- DiLisio, R. P., Mazzeffi, M. A., Bodian, C. A., & Fischer, G. W. (2013). Vocal cord paralysis after aortic surgery. *J Cardiothorac Vasc Anesth*, 27(3), 522-527.
- Dodds, W. J. (1989). The physiology of swallowing. *Dysphagia*, 3(4), 171-178.
- Dong, H., Christopher W. Loomis, and Detlef Bieger. (2001). Vagal afferent input determines the volume dependence of rat esophageal motility patterns. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 281(1), G44-G53.
- Donzelli, J., Brady, S., Wesling, M., & Theisen, M. (2005). Effects of the removal of the tracheotomy tube on swallowing during the fiberoptic endoscopic exam of the swallow (FEES). *Dysphagia*, 20(4), 283-289. doi:10.1007/s00455-005-0027-8
- Donzelli, J., Wesling, M., Brady, S., & Craney, M. (2003). Predictive value of accumulated oropharyngeal secretions for aspiration during video nasal endoscopic evaluation of the swallow. *Annals of Otology, Rhinology and Laryngology*, 112(5), 469-475.
- Doty, R. W. (1951). Influence of stimulus pattern on reflex deglutition. *American Journal of Physiology*, 166(1), 142-158.
- Drakulovic, M. B., Torres, A., Bauer, T. T., Nicolas, J. M., Nogu  , S., & Ferrer, M. (1999). Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *The Lancet*, 354(9193), 1851-1858.

- Easterling, C. S., & Robbins, E. (2008). Dementia and dysphagia. *Geriatric Nursing*, 29(4), 275-285.
- Ebihara, T., Ebihara, S., Maruyama, M., Kobayashi, M., Itou, A., Arai, H., & Sasaki, H. (2006). A randomized trial of olfactory stimulation using black pepper oil in older people with swallowing dysfunction. *J Am Geriatr Soc*, 54(9), 1401-1406.
- El Solh, A., Okada, M., Bhat, A., & Pietrantonio, C. (2003). Swallowing disorders post orotracheal intubation in the elderly. *Intensive Care Med*, 29(9), 1451-1455. doi:10.1007/s00134-003-1870-4
- Elliott, D., Aitken, L. M., Bucknall, T. K., Seppelt, I. M., Webb, S. A., Weisbrodt, L., & McKinley, S. (2013). Patient comfort in the intensive care unit: a multicentre, binational point prevalence study of analgesia, sedation and delirium management. *Critical Care and Resuscitation*, 15(3), 213-219.
- Falconer, J. R., Wu, Z., Lau, H., Suen, J., Wang, L., Pottinger, S., . . . Swift, S. (2014). An Investigation into the Stability and Sterility of Citric Acid Solutions Used for Cough Reflex Testing. *Dysphagia*, 29(5), 622-628.
- Fantus, B. (1912). "Patent medicines"—the pharmacist's duty in regard to them. *Journal of the American Pharmaceutical Association*, 1(2), 104-108.
- Farrell, M. J., Cole, L. J., Chiapoco, D., Egan, G. F., & Mazzone, S. B. (2012). Neural correlates coding stimulus level and perception of capsaicin-evoked urge-to-cough in humans. *NeuroImage*, 61(4), 1324-1335.
- Ferraris, V. A., Ferraris, S. P., Moritz, D. M., & Welch, S. (2001). Oropharyngeal dysphagia after cardiac operations. *Ann Thorac Surg*, 71(6), 1792-1795; discussion 1796.
- Fife, T. A., Butler, S. G., Langmore, S. E., Lester, S., Wright, S. C., Kemp, S., . . . Lintzenich, C. R. (2014). Use of topical nasal anesthesia during flexible endoscopic

- evaluation of swallowing in dysphagic patients. *Annals of Otolaryngology, Rhinology & Laryngology*, 0003489414550153.
- Fontana, G. A., & Lavorini, F. (2006). Cough motor mechanisms. *Respir Physiol Neurobiol*, 152(3), 266-281.
- Fujimura, M., Kamio, Y., Kasahara, K., Bando, T., Hashimoto, T., & Matsuda, T. (1995). Prostanoids and cough response to capsaicin in asthma and chronic bronchitis. *European Respiratory Journal*, 8(9), 1499-1505.
- Fujimura, M., Kasahara, K., Kamio, Y., Naruse, M., Hashimoto, T., & Matsuda, T. (1996). Female gender as a determinant of cough threshold to inhaled capsaicin. *European Respiratory Journal*, 9(8), 1624-1626.
- Goldsmith, T. (2000). Evaluation and Treatment of Swallowing Disorders following Endotracheal Intubation and Tracheostomy. *International Anesthesiology Clinics*, 38(3), 219-242.
- Hafner, G., Neuhuber, A., Hirtenfelder, S., Schmedler, B., & Eckel, H. E. (2008). Fiberoptic endoscopic evaluation of swallowing in intensive care unit patients. *Eur Arch Otorhinolaryngol*, 265(4), 441-446. doi:10.1007/s00405-007-0507-6
- Hansson, L., Wollmer, P., Dahlback, M., & Karlsson, J. A. (1992). Regional Sensitivity of Human Airways to Capsaicin-induced Cough. *American Review of Respiratory Disorders*, 145, 1191-1195.
- Hasegawa, R., & Nishino, T. (1999). Temporal changes in airway protective reflexes elicited by an endotracheal tube in surgical patients anaesthetized with sevoflurane. *Eur J Anaesthesiol*, 16(2), 98-102. doi:10.1046/j.1365-2346.1999.00422.x
- Heffner, J. E. (2010). Swallowing Complications After Endotracheal Extubation : Moving From "Whether" to "How". *Chest*, 137, 509-510. doi:10.1378/chest.09-2477

- Hegland, K. W., Bolser, D. C., & Davenport, P. W. (2012). Volitional Control of Reflex Cough. *Journal of Applied Physiology*, 113(1), 39-46.
- Helmy, A., Vizcaychipi, M., & Gupta, A. (2007). Traumatic brain injury: intensive care management. *British journal of anaesthesia*, 99(1), 32-42.
- Herkel, T., Uvizl, R., Doubravska, L., Adamus, M., Gabrhelik, T., Htoutou Sedlakova, M., . . . Vancouver. (2016). Epidemiology of hospital-acquired pneumonia: Results of a Central European multicenter, prospective, observational study compared with data from the European region. *Biomedical Papers*.
- Hinchey, J. A., Shephard, T., Furie, K., Smith, D., Wang, D., & Tonn, S. (2005). Formal dysphagia screening protocols prevent pneumonia. *Stroke*, 36(9), 1972-1976. doi:10.1161/01.STR.0000177529.86868.8d
- Hogue, C. W., Lappas, G. D., Creswell, L. L., Ferguson, T. B., Sample, M., Pugh, D., . . . Lappas, D. G. (1995). Swallowing Dysfunction after Carciac Operations: Associated adverse outcomes and risk factors including intraoperative transesophageal echocardiography. *Journal Thoracic and Cardiovascular Surgery*, 110(2), 517-522.
- Hovig, B. (1981). Lower respiratory tract infections associated with respiratory therapy and anaesthesia equipment. *The Journal of Hospital Infection*, 2(4), 301-315.
- Hudson, H. M., Daubert, C. R., & Mills, R. H. (2000). The interdependency of protein-energy malnutrition, aging, and dysphagia. *Dysphagia*, 15(1), 31038.
- Hunter, J. D. (2006). Ventilator associated pneumonia. *Postgrad Med J*, 82(965), 172-178. doi:10.1136/pgmj.2005.036905
- Hutchings, H., Eccles, R., Smith, A., & Jawad, M. (1993). Voluntary cough suppression as an indication of symptom severity in upper respiratory tract infections. *European Respiratory Journal*, 6(10), 1449-1454.

- Irwin, R. S., Baumann, M. H., Bolser, D. C., Boulet, L.-P., Braman, S. S., Brightling, C. E., . . . Dicipinigaitis, P. V. (2006). Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *CHEST Journal*, 129(1_suppl), 1S-23S.
- Ji, R., Shen, H., Pan, Y., Wang, P., Liu, G., Wang, Y., . . . Wang, Y. (2013). Novel risk score to predict pneumonia after acute ischemic stroke. *Stroke*, 44(5), 1303-1309.
- Jin, Y. K., Kyoung, H. C., Gi, J. Y., Min, Y. K., & Ju, S. R. (2012). Does Removal of Tracheostomy Affect Dysphagia? A Kinematic Analysis. *Dysphagia*. doi:10.1007/s00455-012-9396-y
- Johnson, P. E., Belafsky, P. C., & Postma, G. N. (2003). Topical nasal anesthesia and laryngopharyngeal sensory testing: a prospective, double-blind crossover study. *Annals of Otology, Rhinology & Laryngology*, 112(1), 14-16.
- Kalf, J., De Swart, B., Bloem, B., & Munneke, M. (2012). Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. *Parkinsonism & related disorders*, 18(4), 311-315.
- Kamei, J. (1996). Role of Opioidergic and Serotonergic Mechanisms in Cough and Antitussives. *Pulm Pharmacol*, 9(5-6), 349-356. doi:<http://dx.doi.org/10.1006/pulp.1996.0046>
- Kastanos, N., Miro, R. E., Perez, A. M., Mir, A. X., & Agusti-Vidal, A. (1983). Laryngotracheal injury due to endotracheal intubation: incidence, evolution, and predisposing factors. A prospective long-term study. *Critical Care Medicine*, 11(5), 362-367.
- Kelly, Leslie, P., Beale, T., Payten, C., & Drinnan, M. J. (2006). Fibreoptic endoscopic evaluation of swallowing and videofluoroscopy: does examination type influence perception of pharyngeal residue severity? *Clinical Otolaryngology*, 31(5).

- Kelly, Shaw, G. M., Brett, C. N., Greenwood, F. M., & Huckabee, M. L. (2016). The effect of titrated fentanyl on suppressed cough reflex in healthy adult volunteers. *Anaesthesia*, 71, 529-534.
- Kertscher, B., Speyer, R., Palmieri, M., & Plant, C. (2014). Bedside screening to detect oropharyngeal dysphagia in patients with neurological disorders: an updated systematic review. *Dysphagia*, 29(2), 204-212.
- Kessler, J. P., & Jean, A. (1985). Identification of the Medullary Swallowing Regions in the Rat. *Experimental Brain Research*, 57(2), 256-263.
- Kollarik, M., & Undem, B. J. (2006). Sensory transduction in cough-associated nerves. *Respir Physiol Neurobiol*, 152(3), 243-254. doi:10.1016/j.resp.2005.12.008
- Kollef, M. H. (1993). Ventilator-associated pneumonia: a multivariate analysis. *JAMA*, 270(16), 1965-1970.
- Kwok, A. M., Davis, J. W., Cagle, K. M., Sue, L., & Kaups, K. L. (2013). Post-extubation dysphagia in trauma patients: it's hard to swallow. *The American Journal of Surgery*, 206(6), 924-928.
- Lamvik, K. M. (2016). Modulation of spontaneous and volitional swallowing: Methodological and behavioural analyses.
- Langmore, S. E., Schatz, K., & Olsen, N. (1988). Fiberoptic endoscopic examination of swallowing safety: a new procedure. *Dysphagia*, 2(4), 216-219.
- Leder, S. B., Cohn, S. M., & Moller, B. A. (1998). Fiberoptic endoscopic documentation of the high incidence of aspiration following extubation in critically ill trauma patients. *Dysphagia*, 13(4), 208-212.
- Leder, S. B., & Murray, J. T. (2008). Fiberoptic endoscopic evaluation of swallowing. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 787-801.

- Leder, S. B., & Ross, D. A. (2010). Confirmation of No Causal Relationship Between Tracheotomy and Aspiration Status: A Direct Replication Study. *Dysphagia*, 25, 35-39. doi:10.1007/s00455-009-9226-z
- Leder, S. B., Ross, D. A., Briskin, K. B., & Sasaki, C. T. (1997). A Prospective, Double-Blind, Randomized Study on the Use of a Topical Anesthetic, Vasoconstrictor, and Placebo During Transnasal Flexible Fiberoptic Endoscopy. *Journal of Speech, Language, and Hearing Research*, 40(6), 1352-1357.
- Lee, Cotterill-Jones, C., & Eccles, R. (2002). Voluntary control of cough. *Pulm Pharmacol Ther*, 15(3), 317-320.
- Lee, & Ho, K. (2013). Sex differences in opioid analgesia and addiction: interactions among opioid receptors and estrogen receptors. *Molecular pain*, 9(1), 1.
- Lee, Kim, D.-K., Seo, K. M., & Kang, S. H. (2014). Usefulness of the simplified cough test in evaluating cough reflex sensitivity as a screening test for silent aspiration. *Annals of rehabilitation medicine*, 38(4), 476-484.
- Lee, & Undem, B. J. (2008). Basic mechanisms of cough: current understanding and remaining questions. *Lung*, 186(1), 10-16.
- Leijten, F., & De Weerd, A. (1994). Critical illness polyneuropathy a review of the literature, definition and pathophysiology. *Clinical neurology and neurosurgery*, 96(1), 10-19.
- Leow, L. P., Beckert, L., Anderson, T., & Huckabee, M.-L. (2012). Changes in chemosensitivity and mechanosensitivity in aging and Parkinson's disease. *Dysphagia*, 27(1), 106-114.
- Lester, S., Langmore, S. E., Lintzenich, C. R., Wright, S. C., Grace - Martin, K., Fife, T., & Butler, S. G. (2013). The effects of topical anesthetic on swallowing during nasoendoscopy. *Laryngoscope*, 123(7), 1704-1708.

- Levine, S., Nguyen, T., Taylor, N., Friscia, M. E., Budak, M. T., Rothenberg, P., . . . Shrager, J. B. (2008). Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*, 358(13), 1327-1335. doi:10.1056/NEJMoa070447
- Lew, C. C. H., Yandell, R., Fraser, R. J., Chua, A. P., Chong, M. F. F., & Miller, M. (2016). Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit A Systematic Review. *Journal of Parenteral and Enteral Nutrition*. doi:0148607115625638
- Lewis, S. C., Li, L., Murphy, M. V., & Klompas, M. (2014). Risk factors for ventilator-associated events: a case-control multivariable analysis. *Critical Care Medicine*, 42(8), 1839-1848.
- Li, J., & Fine, J. (2004). On sample size for sensitivity and specificity in prospective diagnostic accuracy studies. *Statistics in Medicine*, 23(16), 2537-2550. doi:10.1002/sim.1836
- Logemann, J. A. (1998). *Evaluation and Treatment of Swallowing Disorders* (2 ed.). Austin, TX: Pro-Ed.
- Ludlow, C. L., Humbert, I., Saxon, K., Poletto, C., Sonies, B., & Crujido, L. (2007). Effects of surface electrical stimulation both at rest and during swallowing in chronic pharyngeal dysphagia. *Dysphagia*, 22(1), 1-10.
- Macht, Wimbish, Bodine, & Moss. (2013). ICU-acquired swallowing disorders. *Critical Care Medicine*, 41(10), 2396-2405.
- Macht, Wimbish, T., Clark, B. J., Benson, A. B., Burnham, E. J., Williams, A., & Moss, M. (2011). Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. *Critical Care*, 15, 1-9.

- Macht, Wimbish, T., Clark, B. J., Benson, A. B., Burnham, E. L., Williams, A., & Moss, M. (2012). Diagnosis and treatment of post-extubation dysphagia: results from a national survey. *J Crit Care*, 27(6), 578-586. doi:10.1016/j.jcrc.2012.07.016
- Macht, M., Wimbish, T., Clark, B. J., Benson, A. B., Burnham, E. J., Williams, A., & Moss, M. (2011). Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. *Critical Care*, 15, 1-9.
- Mackay, L. E., Morgan, A. S., & Bernstein, B. A. (1999). Swallowing disorders in severe brain injury: risk factors affecting return to oral intake. *Arch Phys Med Rehabil*, 80(4), 365-371.
- Malandraki, G. A., Markaki, V., Georgopoulos, V. C., Psychogios, L., & Nanasc, S. (2016). Postextubation Dysphagia in Critical Patients: A First Report From the Largest Step-Down Intensive Care Unit in Greece. *American Journal of Speech-Language Pathology*, 25(2), 150-156.
- Mann, G., Hankey, G. J., & Cameron, D. (2000). Swallowing disorders following acute stroke: prevalence and diagnostic accuracy. *Cerebrovascular Diseases*, 10(5), 380-386.
- Marik, P. E. (2001). Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*, 344(9), 665-671. doi:10.1056/NEJM200103013440908
- Martin-Harris, B., & Jones, B. (2008). The videofluorographic swallowing study. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 769-785.
- Martino, R., Foley, N., Bhogal, S., Diamant, N., Speechley, M., & Teasell, R. (2005). Dysphagia after stroke incidence, diagnosis, and pulmonary complications. *Stroke*, 36(12), 2756-2763.

- Matsuo, K. P., Jeffrey. (2008). Anatomy and Physiology of Feeding and Swallowing: Normal and Abnormal. *Physical Medicine and Rehabilitation Clinics of North America*, 19(4), 691-707.
- Mazzone, S. B. (2005). An overview of the sensory receptors regulating cough. *Cough*, 1, 2. doi:10.1186/1745-9974-1-2
- Mazzone, S. B., Cole, L. J., Ando, A., Egan, G. F., & Farrell, M. J. (2011). Investigation of the neural control of cough and cough suppression in humans using functional brain imaging. *J Neurosci*, 31(8), 2948-2958. doi:10.1523/JNEUROSCI.4597-10.2011
- Mazzone, S. B., McGovern, A. E., Koo, K., & Farrell, M. J. (2009). Mapping supramedullary pathways involved in cough using functional brain imaging: comparison with pain. *Pulm Pharmacol Ther*, 22(2), 90-96. doi:10.1016/j.pupt.2008.08.003
- Mazzone, S. B., McLennan, L., McGovern, A. E., Egan, G. F., & Farrell, M. J. (2007). Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med*, 176(4), 327-332. doi:10.1164/rccm.200612-1856OC
- Mazzone, S. B., Mori, N., & Canning, B. J. (2005). Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. *J Physiol*, 569(Pt 2), 559-573. doi:10.1113/jphysiol.2005.093153
- McCullough, G., Wertz, R., & Rosenbek, J. (2001). Sensitivity and specificity of clinical/bedside examination signs for detecting aspiration in adults subsequent to stroke. *Journal of communication disorders*, 34(1), 55-72.
- McNicol, E. D., Ferguson, M. C., & Hudcova, J. (2015). Patient controlled opioid analgesia versus non - patient controlled opioid analgesia for postoperative pain. *The Cochrane Library*.

- Miles, & Huckabee, M. L. (2013). Intra- and Inter-rater Reliability for Judgement of Cough Following Citric Acid Inhalation. *International Journal of Speech-Language Pathology*, 15(2), 209-215.
- Miles, Moore, S., McFarlane, M., Lee, F., Allen, J., & Huckabee, M. L. (2013). Comparison of cough reflex test against instrumental assessment of aspiration. *Physiology & Behavior*, 118, 25-31.
- Miles, Zeng, I. S., McLauchlan, H., & Huckabee, M. L. (2013). Cough reflex testing in Dysphagia following stroke: a randomized controlled trial. *J Clin Med Res*, 5(3), 222-233. doi:10.4021/jocmr1340w
- Miles, A. C. (2013). Cough Reflex Testing in Acute Dysphagia Management: Validity, Reliability and Clinical Application.
- Miller, A. J. (2008). The Neurobiology of Swallowing and Dysphagia *Developmental Disabilities Research Reviews*, 14(2), 77-86.
- Monroe, Huckabee, M. L., & Robb, M. (2010). *Citric acid inhalation cough challenge Establishing normative data*. (Master of Science), University of Canterbury.
- Monroe, M. D., Manco, K., Bennett, R., & Huckabee, M. L. (2014). Citric acid cough reflex test: Establishing normative data. *Speech, Language & Hearing*, 17(4), 216-224.
- Morice. (1996). Inhalation Cough Challenge in the Investigation of the Cough Reflex and Antitussives. *Pulm Pharmacol*, 9(5-6), 281-284. doi:<http://dx.doi.org/10.1006/pulp.1996.0036>
- Morice, Fontana, G. A., Belvisi, M. G., Birring, S. S., Chung, K. F., Dicpinigaitis, P. V., . . . Widdicombe, J. (2007). ERS guidelines on the assessment of cough. *Eur Respir J*, 29(6), 1256-1276. doi:10.1183/09031936.00101006
- Morice, Higgins, K., & Yeo, W. (1992). Adaptation of cough reflex with different types of stimulation. *European Respiratory Journal*, 5(7), 841-847.

- Morice, Kastelik, J. A., & Thompson, R. (2001). An overview of methodology of inhalation cough challenge. In C. c. i. t. a. o. c. reflex (Ed.). British Journal of Clinical Pharmacology: John Wiley and Sons.
- Morice, A., Kastelik, J. A., & Thompson, R. J. (2000). Gender differences in airway behaviour. *Thorax*, 55(7), 628-628.
- Morice, A. H., Kastelik, J. A., & Thompson, R. (2001). Cough challenge in the assessment of cough reflex. *Br J Clin Pharmacol*, 52(4), 365-375.
- Morice, A. H., Menon, M. S., Mulrennan, S. A., Everett, C. F., Wright, C., Jackson, J., & Thompson, R. (2007). Opiate Therapy in Chronic Cough. *Am J Respir Crit Care Med*, 175(4), 312-315.
- Murray, J., Langmore, S., Ginsberg, S., & Dostie, A. (1996). The significance of accumulated oropharyngeal secretions and swallowing frequency in predicting aspiration. *Dysphagia*, 11(2), 99-103. doi:10.1007/bf00417898
- Nakajoh, K., Nakagawa, T., Sekizawa, K., Matsui, T., Arai, H., & Sasaki, H. (2000). Relation between incidence of pneumonia and protective reflexes in post-stroke patients with oral or tube feeding. *J Intern Med*, 247(1), 39-42.
- Nakazawa, H., Sekizawa, K., Ujiie, Y., Sasaki, H., & Takishima, T. (1993). Risk of aspiration pneumonia in the elderly. *Chest*, 103(5), 1636-1637.
- Narula, M., McGovern, A. E., Yang, S.-K., Farrell, M. J., & Mazzone, S. B. (2014). Afferent neural pathways mediating cough in animals and humans. *Journal of thoracic disease*, 6(Suppl 7), S712-719.
- Nejla, S., Fujimura, M., & Kamio, Y. (2000). Comparison between tidal breathing and dosimeter methods in assessing cough receptor sensitivity to capsaicin. *Respirology*, 5(4), 337-342.

- Nishino, T. (2013). The swallowing reflex and its significance as an airway defensive reflex. *Frontiers in Physiology*, 3, 489.
- Noordally, S. O., Sohawon, S., De Gieter, M., Bellout, H., & Verougstraete, G. (2011). A Study to Determine the Correlation Between Clinical, Fiber-Optic Endoscopic Evaluation of Swallowing and Videofluoroscopic Evaluations of Swallowing After Prolonged Intubation. *Nutrition in Clinical Practice*, 26(457-462), 457. doi:10.1177/0884533611413769
- Nordang, L., Lindholm, C. E., Larsson, J., & Linder, A. (2016). Early laryngeal outcome of prolonged intubation using an anatomical tube: a double blind, randomised study. *European Archives of Oto-Rhino-Laryngology*, 273(3), 703-708.
- O'Dea, M. B., Langmore, S. E., Krisciunas, G. P., Walsh, M., Zanchetti, L. L., Scheel, R., . . . Butler, S. G. (2015). Effect of lidocaine on swallowing during FEES in patients with dysphagia. *Annals of Otology, Rhinology & Laryngology*, 0003489415570935.
- O'Donoghue, S., & Bagnall, A. (1999). Videofluoroscopic evaluation in the assessment of swallowing disorders in paediatric and adult populations. *Folia phoniatrica et logopaedica*, 51(4-5), 158-171.
- Padovani, A. R., Moraes, D. P., de Medeiros, G. C., de Almeida, T. M., & de Andrade, C. R. F. (2008). Orotracheal intubation and dysphagia: comparison of patients with and without brain damage. *einstein*, 6(3), 343-349.
- Park, Y.-H., Han, H.-R., Oh, B.-M., Lee, J., Park, J.-a., Yu, S. J., & Chang, H. (2013). Prevalence and associated factors of dysphagia in nursing home residents. *Geriatric Nursing*, 34(3), 212-217.
- Pecova, R., Javorkova, N., Kudlicka, J., & Tatar, M. (2007). TUSSIGENIC AGENTS IN THE MEASUREMENT. *Journal of Physiology and Pharmacology*, 58(5), 531-538.

- Peppard, S. B., & Dickens, J. H. (1983). Laryngeal injury following short-term intubation. *Ann Otol Rhinol Laryngol*, 92(4 Pt 1), 327-330.
- Peterson, S. J., Tsai, A. A., Scala, C. M., Sowa, D. C., Sheean, P. M., & Braunschweig, C. L. (2010). Adequacy of oral intake in critically ill patients 1 week after extubation. *Journal of the American Dietetic Association*, 110(3), 427-433.
- Pinto, A., Yanai, M., Sekizawa, K., Aikawa, T., & Sasaki, H. (1995). Conditioned enhancement of cough response in awake guinea pigs. *International archives of allergy and immunology*, 108(1), 95-98.
- Pitts, T., Rose, M. J., Mortensen, A. N., Poliacek, I., Sapienza, C. M., Lindsey, B. G., . . . Bolser, D. C. (2013). Coordination of cough and swallow: a meta-behavioral response to aspiration. *Respir Physiol Neurobiol*, 189(3), 543-551.
- Pizzorni, N., Ginocchio, D., Mozzanica, F., Roncoroni, L., Scarponi, L., & Schindler, A. (2014). Head and neck diseases and disorders causing oropharyngeal dysphagia. *Journal of Gastroenterology and Hepatology Research*, 3(10), 1272-1280.
- Ponfick, M., Linden, R., & Nowak, D. A. (2015). Dysphagia—A common, transient symptom in critical illness polyneuropathy: a fiberoptic endoscopic evaluation of swallowing study. *Critical Care Medicine*, 43(2), 365-372.
- Postma, G. N., McGuirt, W. F., Sr., Butler, S. G., Rees, C. J., Crandall, H. L., & Tansavatdi, K. (2007). Laryngopharyngeal abnormalities in hospitalized patients with dysphagia. *Laryngoscope*, 117(10), 1720-1722. doi:10.1097/MLG.0b013e31811ff906
- Potts, R. G., Zaroukian, M. H., Guerrero, P. A., & Baker, C. D. (1993). Comparison of blue dye visualization and glucose oxidase test strip methods for detecting pulmonary aspiration of enteral feedings in intubated adults. *Chest*, 103(1), 117-121.
- Pounsford, J., & Saunders, K. (1985). Diurnal variation and adaptation of the cough response to citric acid in normal subjects. *Thorax*, 40(9), 657-661.

- Ramsey, D. J., Smithard, D. G., & Kalra, L. (2003). Early assessments of dysphagia and aspiration risk in acute stroke patients. *Stroke*, 34(5), 1252-1257.
- Rao, N., Brady, S. L., Chaudhuri, G. D., J.J., & Wesling, M. W. (2003). Gold-standard? Analysis of the videofluoroscopic and fiberoptic endoscopic swallow examinations. *Journal of Applied Research*, 3(1), 1-8.
- Redington, A. E., Morice, A. H., & Kastelik, J. A. (2005). Acid Inhalation Cough Challenge *Acute and Chronic Cough* (pp. 177-194): CRC Press.
- Reinarz, J. A., Pierce, A. K., Mays, B. B., & Sanford, J. P. (1965). The potential role of inhalation therapy equipment in nosocomial pulmonary infection. *The Journal of Clinical Investigation*(44), 831-839.
- Research, U. S. D. o. H. a. H. S. F. a. D. A. C. f. D. E. a. (2002). Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation. Retrieved from <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf>
- Robbins, J., Kays, S. A., Gangnon, R. E., Hind, J. A., Hewitt, A. L., Gentry, L. R., & Taylor, A. J. (2007). The effects of lingual exercise in stroke patients with dysphagia. *Arch Phys Med Rehabil*, 88(2), 150-158.
- Rosenbek, J. C., Robbins, J. A., Roecker, E. B., Coyle, J. L., & Wood, J. L. (1996). A penetration-aspiration scale. *Dysphagia*, 11(2), 93-98.
- Rousou, J. A., Tighe, D. A., Garb, J. L., Krasner, H., Engelman, R. M., Flack, J. E., 3rd, & Deaton, D. W. (2000). Risk of dysphagia after transesophageal echocardiography during cardiac operations. *Ann Thorac Surg*, 69(2), 486-489; discussion 489-490.

- Safdar, N., Dezfulian, C., Collard, H. R., & Saint, S. (2005). Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med*, 33(10), 2184-2193.
- Saunders, J., & Smith, T. (2010). Malnutrition: causes and consequences. *Clinical Medicine*, 10(6), 624-627.
- Scannapieco, F. A. (2006). Pneumonia in nonambulatory patients: the role of oral bacteria and oral hygiene. *The American Dental Association*, 137, S21-S25.
- Schatz, K., Langmore, S., & Olsen, N. (1991). Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. *Otology, Rhinology & Laryngology*, 100(8), 678-681.
- Scheel, R., Langmore, S., McNally, E., Walsh, M., Reynolds, M., Golan, H., . . . Noordzij, J. P. (2009). *Swallowing Post Extubation in Patients with No Premorbid Dysphagia*. Presentation. Retrieved from http://www.asha.org/Events/convention/handouts/2009/2000_Scheel_Rebecca/
- Scheel, R., Pisegna, J. M., McNally, E., Noordzij, J. P., & Langmore, S. E. (2016). Endoscopic Assessment of Swallowing After Prolonged Intubation in the ICU Setting. *Annals of Otology, Rhinology and Laryngology*, 125(1), 43-52.
- Schenning, K. J., & Deiner, S. G. (2015). Postoperative delirium: a review of risk factors and tools of prediction. *Current Anesthesiology Reports*, 5(1), 48-56.
- Schröter-Morasch, H., Bartolome, G., Troppmann, N., & Ziegler, W. (1999). Values and limitations of pharyngolaryngoscopy (transnasal, transoral) in patients with dysphagia. *Folia phoniatrica et logopaedica*, 51(4-5), 172-182.
- Sekizawa, K., Ujiie, Y., Itabashi, S., Sasaki, H., & Takishima, T. (1990). Lack of cough reflex in aspiration pneumonia. *Lancet*, 335(8699), 1228-1229.
- Selim, M. (2007). Perioperative Stroke. *New England Journal of Medicine*, 356(7), 706-713.

- Shannon, R., Baekey, D. M., Morris, K. F., Nuding, S. C., Segers, L. S., & Lindsey, B. G. (2004). Production of reflex cough by brainstem respiratory networks. *Pulm Pharmacol Ther*, 17(6), 369-376. doi:10.1016/j.pupt.2004.09.022
- Shehabi, Y., Bellomo, R., Reade, M. C., Bailey, M., Bass, F., Howe, B., . . . Webb, S. (2013). Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study. *Critical Care Medicine*, 41(8), 1983-1991.
- Sider, L., Mintzer, R. A., Deschler, T. W., Kim, K. S., & Weinberg, P. E. (1983). Control of swallowing by use of topical anesthesia during digital subtraction angiography. *Radiology*, 148(2), 563-564.
- Simpson, H., Clancy, M., Goldfrad, C., & Rowan, K. (2005). Admissions to intensive care units from emergency departments: a descriptive study. *Emergency Medicine Journal*, 22(6), 423-428.
- Sitkauskiene, B., & Dicpinigaitis, P. V. (2010). Effect of smoking on cough reflex sensitivity in humans. *Lung*, 188(1), 29-32.
- Sitkauskiene, B., Stravinskaite, K., Sakalauskas, R., & Dicpinigaitis, P. V. (2007). Changes in cough reflex sensitivity after cessation and resumption of cigarette smoking. *Pulm Pharmacol Ther*, 20(3), 240-243.
- Skoretz, S. A., Flowers, H. L., & Martino, R. (2010). The incidence of dysphagia following endotracheal intubation: a systematic review. *Chest*, 137(3), 665-673. doi:10.1378/chest.09-1823
- Soh, S., Park, W. K., Kang, S. W., Lee, B. R., & Lee, J. R. (2014). Sex differences in remifentanyl requirements for preventing cough during anesthetic emergence. *Yonsei medical journal*, 55(3), 807-814.

- Stauffer, J. L., Olson, D. E., & Petty, T. L. (1981). Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. *Am J Med*, 70(1), 65-76.
- Steele, C. M., Bailey, G. L., Chau, T., Molfenter, S. M., Oshalla, M., Waito, A. A., & Zoratto, D. C. (2011). The relationship between hyoid and laryngeal displacement and swallowing impairment. *Clinical Otolaryngology*, 36(1), 30-36.
- Steele, C. M., & Miller, A. J. (2010). Sensory input pathways and mechanisms in swallowing: a review. *Dysphagia*, 25(4), 323-333. doi:10.1007/s00455-010-9301-5
- Stephens, R. E., Addington, W. R., & Widdicombe, J. G. (2003). Effect of acute unilateral middle cerebral artery infarcts on voluntary cough and the laryngeal cough reflex. *American journal of physical medicine & rehabilitation*, 82(5), 379-383.
- Sugiyama, Y., Shiba, K., Nakazawa, K., Suzuki, T., Umezaki, T., Ezure, K., . . . Hisa, Y. (2011). Axonal projections of medullary swallowing neurons in guinea pigs. *Journal of Comparative Neurology*, 519(11), 2193-2211.
- Tadie, J. M., Behm, E., Lecuyer, L., Benhmamed, R., Hans, S., Brasnu, D., . . . Guerot, E. (2010). Post-intubation laryngeal injuries and extubation failure: a fiberoptic endoscopic study. *Intensive Care Med*, 36(6), 991-998. doi:10.1007/s00134-010-1847-z
- Tanaka, A., Isono, S., Ishikawa, T., & Nishino, T. (2005). Laryngeal reflex before and after placement of airway interventions: endotracheal tube and laryngeal mask airway. *Anesthesiology*, 102(1), 20-25.
- Teismann, I. K., Steinstraeter, O., Stoeckigt, K., Suntrup, S., Wollbrink, A., Pantev, C., & Dziawas, R. (2007). Functional oropharyngeal sensory disruption interferes with the cortical control of swallowing. *BMC Neurosci*, 8, 62. doi:10.1186/1471-2202-8-62

- Terzano, C., Petroianni, A., Parola, D., & Ricci, A. (2007). Compressor/nebulizers differences in the nebulization of corticosteroids. The CODE study (Corticosteroids and Devices Efficiency). *European review for medical and pharmacological sciences*, 11(4), 225.
- Tolep, K., Getch, C. L., & Criner, G. J. (1996). Swallowing dysfunction in patients receiving prolonged mechanical ventilation. *Chest*, 109(1), 167-172.
- Ushioda, T., Watanabe, Y., Sanjo, Y., Yamane, G.-y., Abe, S., Tsuji, Y., & Ishiyama, A. (2012). Visual and auditory stimuli associated with swallowing activate mirror neurons: a magnetoencephalography study. *Dysphagia*, 27(4), 504-513.
- Van Daele, D. J., McCulloch, T. M., Palmer, P. M., & Langmore, S. E. (2005). Timing of glottic closure during swallowing: a combined electromyographic and endoscopic analysis. *Annals of Otology, Rhinology & Laryngology*, 114(6), 478-487.
- Vila, J., Bosque, M. D., Garcia, M., Palomar, M., Quesada, P., & Ramis, B. (1997). Endoscopic evolution of laryngeal injuries caused by translaryngeal intubation. *Eur Arch Otorhinolaryngol*, 254 Suppl 1, S97-100.
- Wakasugi, Tohara, H., Hattori, F., Motohashi, Y., Nakane, A., Goto, S., . . . Uematsu, H. (2008). Screening test for silent aspiration at the bedside. *Dysphagia*, 23(4), 364-370. doi:10.1007/s00455-008-9150-7
- Wakasugi, Tohara, H., Nakane, A., Murata, S., Mikushi, S., Susa, C., . . . Uematsu, H. (2014). Usefulness of a handheld nebulizer in cough test to screen for silent aspiration. *Odontology*, 102(1), 76-80.
- Wang, C. M., Shieh, W. Y., Chen, J. Y., & Wu, Y. R. (2015). Integrated non - invasive measurements reveal swallowing and respiration coordination recovery after unilateral stroke. *Neurogastroenterology & Motility*, 27(10), 1398-1408.

- Warnecke, T. (2009). The safety of fiberoptic endoscopic evaluation of swallowing in acute stroke patients. *Stroke*, 40(2), 482-486.
- Warnecke, T., Ritter, M. A., Kröger, B., Oelenberg, S., Teismann, I., Heuschmann, P. U., . . . Dziawas, R. (2009). Fiberoptic Endoscopic Dysphagia Severity Scale Predicts Outcome after Acute Stroke. *Cerebrovascular Diseases*, 28(3), 283-289. doi:<http://dx.doi.org/10.1159/000228711>
- Watando, A., Ebihara, S., Ebihara, T., Okazaki, T., Takahashi, H., Asada, M., & Sasaki, H. (2004). Daily oral care and cough reflex sensitivity in elderly nursing home patients. *CHEST Journal*, 126(4), 1066-1070.
- Weinstein, R. A., Bonten, M. J., Kollef, M. H., & Hall, J. B. (2004). Risk factors for ventilator-associated pneumonia: from epidemiology to patient management. *Clinical Infectious Diseases*, 38(8), 1141-1149.
- Weissman, C. (1999). Pulmonary function after cardiac and thoracic surgery. *Anesthesia & Analgesia*, 88(6), 1272-1279.
- Whited, R. E. (1984). A prospective study of laryngotracheal sequelae in long-term intubation. *Laryngoscope*, 94(3), 367-377.
- Widdicombe, Addington, W. R., Fontana, G. A., & Stephens, R. E. (2011). Voluntary and reflex cough and the expiration reflex; implications for aspiration after stroke. *Pulm Pharmacol Ther*, 24(3), 312-317. doi:10.1016/j.pupt.2011.01.015
- Widdicombe, Eccles, R., & Fontana, G. (2006). Supramedullary influences on cough. *Respir Physiol Neurobiol*, 152(3), 320-328. doi:10.1016/j.resp.2006.02.018
- Widdicombe, J. (2001). Airway receptors. *Respir Physiol*, 125(1-2), 3-15.
- Wong, C. H., Matai, R., & Morice, A. H. (1999). Cough induced by low pH. *Respir Med*, 93(1), 58-61.

Yamanda, S., Ebihara, S., Ebihara, T., Yamasaki, M., Asamura, T., Asada, M., . . . Arai, H.

(2008). Impaired urge-to-cough in elderly patients with aspiration pneumonia. *Cough*,

4, 11. doi:10.1186/1745-9974-4-11

12. APPENDICES

- A. Information Sheet and Consent Form for Relative/Whanau/Friend
- B. Information Sheet and Consent Form for Participant
- C. Record of Participants
- D. Screening Log
- E. Case Report Form
- F. VES Rating Form

APPENDIX A – INFORMATION SHEET FOR RELATIVE/WHĀNAU/FRIEND



Information Sheet for Relative, Whānau Member or Friend

Study title: CRAIn II

Locality: C&CDHB

Ethics committee ref.: 14/CEN

Lead investigator: Molly Kallesen

Contact phone number: 04 80

Your relative/whānau member/friend is invited to take part in a study on how breathing tubes affect swallowing. Whether or not your relative/whānau member/friend takes part is your choice. If you don't want your relative/whānau member/friend to take part, you don't have to give a reason, and it won't affect the care they receive. If you do want them to take part now, but change your mind later, you can pull them out of the study at any time.

This Participant Information Sheet will help you decide if you would like for your relative/whānau member/friend to take part. It sets out why we are doing the study, what participation would involve, what the benefits and risks might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will agree for your relative/ whānau member/friend to participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this. Unfortunately, this study does not have funding to provide an interpreter for you or your relative/whānau member/friend.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Information Sheet for Relative, Whānau Member or Friend and the Consent Form to keep.

This document is seven pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

Cough is the body's way of clearing saliva, food or fluid from your airway. Material can get into the lungs and cause a serious lung infection if the cough reflex is absent or weak. Sometimes people have trouble coughing and swallowing after they've had a breathing tube. This can slow recovery and healing.

The aim of this project is to find out if a cough screening test is a useful way to predict how you protect your airway when eating and drinking. To do this we will compare a new cough screening test to a well established test of swallowing. The new cough screening test is quicker, easier and cheaper than the traditional test and is used routinely with people who have had a stroke. However, we don't know how reliable it is for patients in ICU who have had breathing tubes. We want to know if this cough screening test can be used to identify ICU patients who are at high risk for getting an infection in the lungs. We can then provide the best and safest treatment to avoid an infection.

This study is sponsored by Capital and Coast DHB (C&CDHB) and the University of Canterbury (UC). The lead investigator is a Speech-Language Therapist at C&CDHB and a student at UC. This project has been reviewed and approved by the Central Health and Disability Ethics Committee, University of Canterbury Human Ethics Committee (Private Bag 4800, Christchurch, email human-ethics@canterbury.ac.nz) and Capital & Coast District Health Board Research Advisory Group – Maori.

If you have any questions about this study, you can contact the lead investigator using the details below.

Molly Kallesen (Lead Investigator)
04 806 2345
molly.kallesen@ccdhb.org.nz

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You are being asked to agree to your relative/whānau member/friend taking part in this study because they have had a breathing tube (intubation) as part of their treatment in ICU. In order to take part, they need to have had the breathing tube removed within the previous twelve hours, be older than 18 and able to eat and drink at the time the lead investigator comes to see them. If they have had serious life-threatening nosebleeds, recently broken bones in the face or skull, are not for active treatment or have had a tracheostomy they will not be able to take part. They must be able to give consent or have a relative, whānau member or friend who can consent on their behalf. A total of 108 participants will be enrolled, half with a surgical reason for admission and half with a non-surgical diagnosis.

If you agree for your relative/whānau member/friend to take part in the study, the lead investigator will come see them within 24 hours of having their breathing tube removed. If your relative/whānau member/friend is able to make decisions at this time they will be asked to agree to the study themselves and will have the right to say no. If they are not able to

make decisions the researcher will refer to your decision. However, if it's obvious that your relative/whānau member/friend does not want to take part (e.g. they push the tube away or shake their head no), the researcher will stop.

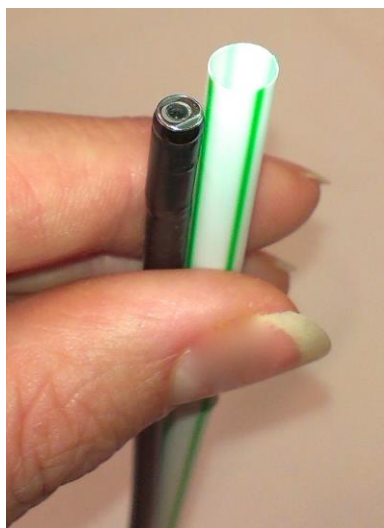
If your relative/whānau member/friend agrees, they will have a cough reflex test (CRT) and videoendoscopy of swallowing (VES). The two tests are described below. The VES immediately follows the CRT and both should be finished in at total of 30 to 45 minutes.

Cough Reflex Test (CRT):

- The researcher will place a small amount of liquid into a nebuliser. The nebuliser is a small device that turns the liquid into mist so it can be inhaled. The mist is delivered through a mask that the researcher holds up to your relative/whānau member/friend's mouth and nose. They will be asked to breathe the mist in for 15 seconds.
- The mist may make them feel like coughing. The researcher will ask them to try not to cough. The researcher will record any coughs.
- After 15 seconds the mask will be taken off and your relative/whānau member/friend can relax. The test may need to be repeated several more times.

Videoendoscopy (VES):

a
a



- Your relative/whānau member/friend will be asked to sit still and relax.
- The researcher will pass a thin tube (4.9mm) through their nose with a tiny camera at the tip. This should take about 10 to 15 seconds. The tube is well lubricated so that it can pass smoothly and easily through the nose. You can see a picture of the tube below next to normal drinking straw, which is 6mm across. The camera takes a video, which is recorded on DVD. If you're present, you will also be able to see the video on the screen.
- Once the camera is in place the researcher may ask your relative/whānau member/friend to make some sounds, swallow and cough. On the video the researcher will be able to see how well the structures of the throat and voice box are working.
- The researcher will then ask them to swallow a few bites and sips of food that has been coloured blue or green. The researcher will be looking to see if the food and drink go down the way they should.
- The camera will then be gently removed and the test is finished.

After these two tests are finished, the researcher will collect some information from the medical notes about your relative/whānau member/friend's reason for being in hospital and

details about the breathing tube and pain medication. Your relative/whānau member/friend will not need to do anything more for the study.

You may decide that you do not want your relative/whānau member/friend to participate in the study. In that case, the speech-language therapist may still assess them if the nurses or doctors suspect they are having swallowing problems. They may have the tests described above as part of routine care if the team think this would help them make decisions about treatment and if your relative/whānau member/friend agrees. This is not part of the study and any test results will not be recorded or stored outside of their medical record.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

The cough test has been used for many years. No harmful effects from cough testing have been reported. Your relative/whānau member/friend may feel slightly tightness in their chest when inhaling the mist. Coughing may feel uncomfortable if they've just had surgery. Coughing is important for recovery and the doctors and nurses will encourage your relative/whānau member/friend to cough.

Videoendoscopy is used routinely by speech-language therapists and doctors and is very safe. A trained person will monitor your relative/whānau member/friend closely throughout the testing. The first 10 to 15 seconds when the camera is being positioned can be mildly to moderately uncomfortable, but should not be painful. A very small number of people have mild nosebleeds or faint during the test. If your relative/whānau member/friend finds the VES too uncomfortable they can ask to stop.

The videoendoscopy may identify that your relative/whānau member/friend has swallowing problems. This will be useful information for making sure they have the best recovery possible. The researcher may feel that they would benefit from further testing or advice about their swallowing. In this case, the researcher will ask you or your relative/whānau member/friend's permission to share this information with the people treating them. The researcher or another speech-language therapist may come to visit your relative/whānau member/friend again to help manage any swallowing problems. This is part of usual ICU treatment and is not part of the study. The researcher will be very clear if she is seeing your relative/whānau member/friend for a reason unrelated to the study.

WHO PAYS FOR THE STUDY?

All costs for this study are covered by the University of Canterbury and C&CDHB. It will not cost you or your relative/whānau member/friend anything to participate. They will not receive any payment for taking part.

WHAT IF SOMETHING GOES WRONG?

If your relative/whānau member/friend were injured in this study, which is unlikely, they would be eligible for compensation from ACC just as they would be if they were injured in an accident at work or at home. They will have to lodge a claim with ACC, which may take

some time to assess. If their claim is accepted, they will receive funding to assist in their recovery.

If your relative/whānau member/friend has private health or life insurance, you may wish to check with their insurer that taking part in this study won't affect their cover.

WHAT ARE MY RIGHTS?

Participation: If you do agree for your relative/whānau member/friend to take part in this study you, or your relative/whānau member/friend, can stop at any time. You do not need to give a reason for stopping. Stopping will not change the care they receive. Their participation in the study will be stopped should any harmful effects appear.

Confidentiality: The staff involved in treating your relative/whānau member/friend will know whether or not your relative/whānau member/friend is participating in this study. Any identifiable information that is collected about your relative/whānau member/friend in connection with this study will remain confidential and will be shared only with your permission, except as required by law. The identity of your relative/whānau member/friend will remain confidential in any study reports, publications or presentations.

Questions: You may have a friend, family, or whānau support person to help you understand the risks and benefits of this study. They are welcome to speak to the researcher with your permission. Please contact the researcher listed on the front page of this information sheet if you have any questions.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

This form and other paperwork will be stored in a locked cupboard on the ICU or password-protected computer and will only be available to the researcher and supervisors of the study. All records will be stored for a period of ten years then sent to the national archive. The same investigator may use information collected in this study in future studies that have ethical approval from the New Zealand Health and Disability Ethics Committee.

You and your relative/whānau member/friend can have copies of any publication of from this research. You can also choose to have someone discuss the results of the study with you and/or your relative/whānau member/friend. It will likely be one year before any information is available. Please let the researcher know if you would like her to share the results with you.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact the study supervisor at:

Dr. Maggie-Lee Huckabee (Supervisor)
03 378 6070
maggie-lee.huckabee@canterbury.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

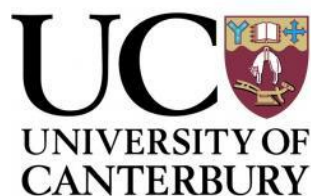
Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

For Maori health support please contact :

Whānau Care Services
04 806 0948
wcs@ccdhb.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz



Consent Form

Please tick to indicate you consent to the following *(Add or delete as appropriate)*

I have read, or have had read to me, and I understand the Information Sheet for Relative, Whānau Member of Friend.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
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I have been given sufficient time to consider whether or not to participate in this study.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
--	------------------------------	-----------------------------

I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

I understand that taking part in this study is voluntary (my choice) and that I, or my relative/whānau member/friend, may withdraw from the study at any time without this affecting the medical care of my relative/whānau member/friend.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
--	------------------------------	-----------------------------

I consent to the research staff collecting and processing my relative/whānau member/friend's information, including information about their health.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

If I decide to withdraw my relative/whānau member/friend from the study, I agree that the information collected about them up to the point when I withdraw may continue to be processed.

Yes ☐ No ☐

I consent to the medical team being informed about my participation in the study and of any significant abnormal results obtained during the study.

Yes ☐ No ☐

I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relative/whānau member/friend's relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

Yes ☐ No ☐

I understand that my relative/whānau member/friend's participation in this study is confidential and that no material, which could identify my relative/whānau member/friend, will be used in any reports on this study.

Yes ☐ No ☐

I know who to contact if I have any questions about the study in general.

Yes ☐ No ☐

I wish to receive a summary of the results from the study.

Yes ☐ No ☐

Declaration by Relative/Whānau member/Friend:

I hereby consent for my relative/whānau member/friend to take part in this study.

Name:

Relationship:

Signature:

Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant's relative/whānau member/friend, and have answered their questions about it.

I believe that the relative/whānau member/friend understands the study and has given informed consent for their relative/whānau member/friend to participate.

Researcher's name:

Signature:

Date:

APPENDIX B – PARTICIPANT INFORMATION SHEET



Participant Information Sheet

Study title: CRAIn II

Locality: C&CDHB

Ethics committee ref.: 14/CEN

Lead investigator: Molly Kallesen

Contact phone number: 04 80

You are invited to take part in a study on how breathing tubes affect swallowing. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what participation would involve, what the benefits and risks might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this. This study does not have funding to provide an interpreter for you.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is seven pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

Cough is the body's way of clearing saliva, food or fluid from your airway. Material can get into the lungs and cause a serious lung infection if the cough reflex is absent or weak. Sometimes people have trouble coughing and swallowing after they've had a breathing tube. This can slow recovery and healing.

The aim of this project is to find out if a cough screening test is an accurate way to predict how you protect your airway when eating and drinking. To do this we will compare a new cough screening test to a well established test of swallowing. The new cough screening test is quicker, easier and cheaper than the traditional test and is used routinely with people who have had a stroke. However, we don't know how reliable it is for patients in ICU who have had breathing tubes. We want to know if this cough screening test can be used to identify ICU patients who are at high risk for getting an infection in the lungs. We can then provide the best and safest treatment to avoid an infection.

This study is sponsored by Capital and Coast DHB (C&CDHB) and the University of Canterbury (UC). The lead investigator is a Speech-Language Therapist at C&CDHB who is also a student at UC. This project has been reviewed and approved by the Central Health and Disability Ethics Committee, University of Canterbury Human Ethics Committee (Private Bag 4800, Christchurch, email human-ethics@canterbury.ac.nz) and Capital & Coast District Health Board Research Advisory Group – Maori.

If you have any questions about this study, you can contact the lead investigator using the details below.

Molly Kallesen (Lead Investigator)

04 806 2345

molly.kallesen@ccdhub.org.nz

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You are being asked to take part in this study because you have had a breathing tube (intubation) as part of your treatment in ICU. In order to take part, you need to have had the breathing tube removed within the previous twelve hours, be older than 18 and able to eat and drink at the time the lead investigator comes to see you. If you have had serious life-threatening nosebleeds, recently broken bones in the face or skull, are not for active treatment or have had a tracheostomy you will not be able to take part. You must be able to give consent or have a relative, whānau member or friend who can consent on your behalf. A total of 108 participants will be enrolled, half with a surgical reason for admission and half with a non-surgical diagnosis.

The lead investigator will come see you within 24 hours of having the breathing tube removed. If you agree to take part in the study, you will have a cough reflex test (CRT) and videoendoscopy of swallowing (VES). The two tests are described below. The VES immediately follows the CRT and both should be finished in at total of 30 to 45 minutes.

Cough Reflex Test (CRT):

- The researcher will place a small amount of liquid into a nebuliser. The nebuliser is a small, electronic device that turns the liquid into mist so it can be inhaled. The mist is delivered through a mask that the researcher holds up to your mouth and nose. You will be asked to breathe the mist in for 15 seconds.
- The mist may make you feel like coughing. The researcher will ask you to try not to cough. The researcher will record any coughs.

- After 15 seconds the mask will be taken off and you can relax. The test may need to be repeated several more times.

Videoesndoscopy (VES):

- You will be asked to sit still and relax.
- The researcher will pass a thin tube (4.9mm) through your nose with a tiny camera at the tip. This should take about 10 to 15 seconds. The tube is well lubricated so that it can pass smoothly and easily through the nose. You can see a picture of the tube



below. The camera takes a video, which is recorded on a DVD. You may be able to see the video on the screen.

- Once the camera is in place the researcher may ask you to make some sounds, swallow and cough. On the video the researcher will be able to see how well the structures of the throat and voice box are working.
- The researcher will then ask you to swallow a few bites and sips of food that has been coloured blue or green. The researcher will be looking to see if the food and drink go down the way they should.
- The camera will then be gently removed and the test is finished.

After these two tests are finished, the researcher will collect some information from the medical notes about why you are in hospital and details about the breathing tube and pain medication. You will not need to do anything more for the study.

You may decide that you do not want to participate in the study. In that case, a speech-language therapist may still assess you if the nurses or doctors suspect you are having swallowing problems. You may have the tests described above as part of routine care if the team think this would help them make decisions about your treatment and if you agree. This is not part of the study and any test results will not be recorded or stored outside of your medical record.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

The cough test has been used for many years. No harmful effects from cough testing have been reported. You may feel slight tightness in your chest when inhaling the mist. Coughing may feel uncomfortable if you've just had surgery. Coughing is important for recovery and the doctors and nurses will encourage you to cough.

Videoesndoscopy is used routinely by speech-language therapists and doctors and is very safe. A trained person will monitor you closely throughout the testing. The first 10 to 15 seconds when the camera is being positioned can be mildly to moderately uncomfortable, but

should not be painful. A very small number of people have mild nosebleeds or faint during the test. If you find the VES too uncomfortable you can ask to stop.

The videoendoscopy may identify that you have swallowing problems. This will be useful information for making sure you have the best recovery possible. The researcher may feel that you would benefit from further testing or advice about your swallowing. In this case, the researcher will ask your permission to share this information with the people treating you. The researcher or another speech-language therapist may come to visit you again to help manage any swallowing problems. This is part of usual ICU treatment and is not part of the study. The researcher will be very clear if she is seeing you for a reason unrelated to the study.

WHO PAYS FOR THE STUDY?

All costs for this study are covered by the University of Canterbury and C&CDHB. It will not cost you anything to participate. You will not receive any payment for taking part.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Participation: If you do agree to take part in this study you can stop at any time. You do not need to give a reason for stopping. Stopping will not change the care you receive. Your participation in the study will be stopped should any harmful effects appear.

Confidentiality: The staff involved in treating you will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be shared only with your permission, except as required by law. Your identity will remain confidential in any study reports, publications or presentations.

Questions: You may have a friend, family, or whanau support person to help you understand the risks and benefits of this study. They are welcome to speak to the researcher with your permission. Please contact the researcher listed on the front page of this information sheet if you have any questions.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

This form and other paperwork will be stored in a locked cupboard on the ICU or password-protected computer and will only be available to the researcher and supervisors of the study. All records will be stored for a period of ten years then sent to the national archive. The same investigator may use information collected in this study in future studies that have ethical approval from the New Zealand Health and Disability Ethics Committee.

You can have copies of any publication of from this research. You can also choose to have someone discuss the results of the study with you. It will likely be more than one year before any information is available. Please let the researcher know if you would like her to share the results with you.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact the study supervisor at:

Dr. Maggie-Lee Huckabee (Supervisor)
03 378 6070
maggie-lee.huckabee@canterbury.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

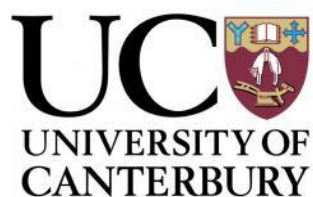
Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

For Maori health support please contact :

Whānau Care Services
04 806 0948
wcs@ccdhub.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdec@moh.govt.nz



Participant Consent Form

Please tick to indicate you consent to the following *(Add or delete as appropriate)*

I have read, or have had read to me, and I understand the Participant Information Sheet.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
--	------------------------------	-----------------------------

I have been given sufficient time to consider whether or not to participate in this study.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
--	------------------------------	-----------------------------

I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting the my medical care.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

I consent to the research staff collecting and processing my information, including information about my health.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
--	------------------------------	-----------------------------

If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to	Yes <input type="checkbox"/>	No <input type="checkbox"/>
---	------------------------------	-----------------------------

be processed.

I consent to the medical team being informed about my participation

in the study and of any significant abnormal results obtained during the study. Yes ☐ No ☐

I agree to an approved auditor appointed by the New Zealand

Health and Disability Ethic Committees, or any relevant regulatory

authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of

the information recorded for the study. Yes ☐ No ☐

I understand that my participation in this study is confidential and

that no material, which could identify me, will be used in any reports on this study. Yes ☐ No ☐

I know who to contact if I have any questions about the study in

general. Yes ☐ No ☐

I wish to receive a summary of the results from the study.

Yes ☐ No ☐

Declaration by Participant:

I hereby consent to take part in this study.

Name:

Relationship:

Signature:

Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant and have answered their questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature:

Date:

APPENDIX D – SCREENING LOG

[illegible]

APPENDIX E – CASE REPORT FORM

Patient Initials:		Date of Enrollment:	
PIN:		Date of Completion:	
Demographics:			
Date of Birth:			
Age:			
Gender:			
Ethnicity:			
Exclusion Criteria:			
History of severe nosebleeds	Yes (exclude)	No	
Facial or base of skull fracture < 4 weeks	Yes (exclude)	No	
Patient or NOK able to provide consent?	Yes	No (exclude)	
GCS	<13	≥13	
Ok for oral intake?	Yes	No	
Patient palliative?	Yes (exclude)	No	
Comments on above:			
Covariates:			
Date & time of intubation:	/ /		

Date & time of extubation:	/ /	
Diagnosis type:	Surgical	Non-surgical
Primary diagnosis:		
Apache III score:		
Opiates in previous 24 hours:	Type:	Amt:

Patient ID:	
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COUGH REFLEX TEST:			
Record for each trial A = absent, W = weak, S = strong pass, X = not administered			
Instruct the participant to try not to cough			
Date of CRT			
Time of CRT			
Concentration	Presentation 1	Presentation 2	Presentation 3
____ mol / saline			
____ mol / saline			
____ mol / saline			
____ mol / saline			
Subject Threshold = _____ OR Absent Cough			
Adverse events: NO YES (See adverse event record)			
Comments:			

Videoendoscopic Evaluation of Swallowing (VES):	
	5 controlled sips thin fluid
If stopped, comment why incomplete:	
	150mls thin fluid continuous drinking
If stopped, comment why incomplete:	

APPENDIX H – VES RATING FORM

PIN:		Date reviewed:			
Date of FEES:		Reviewer:			
Aspiration (circle one below)		Cough (circle one below)			
Present	Absent	Trace	Present Absent		
Secretions Rating (circle)		0	1	2	3
Comment on secretions:					